NEW METHODOLOGIES AND APPROACHES TO REACTION DISCOVERY IN TRANSITION METAL CATALYSIS

BY

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DISSERTATION

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ABSTRACT

A series of synthetic methods have been developed based upon iridium-catalyzed borylation of aromatic and heteroaromatic C-H bonds. A general, one-pot method for alkylation of arenes with the site-selectivity controlled by steric effects as opposed to electronic effects via Ir-catalyzed C-H borylation followed by Pd- or Ni-catalyzed coupling with allylic, benzylic or unactivated alkyl electrophiles has been developed. Simple palladium catalysts enable the coupling of aryl boronate esters formed from iridium-catalyzed C-H borylation to be coupled with various allylic halides, allylic carboxylates and benzylic halides. Nickel catalysts bearing diamine or phenanthroline-based ligands have been used to couple these aryl boronate esters with primary and secondary, unactivated alkyl halides. *Meta*-selective alkylation of a broad scope of arenes with various electronic properties and functional groups, including aryl halides, esters, amides, ethers and ketones, has been demonstrated with good yield. This methodology has also been used to perform a one-pot total synthesis of elemicin, a natural product with potential biological activity, and a formal synthesis of an HIV drug candidate.

In another study, a new approach to Suzuki-Miyaura coupling of potentially unstable organoboronates was developed. Biaryls in which one or more of the aryl rings are heteroarenes or fluorinated arenes are found widely in medicinal chemistry and materials science, but are challenging to prepare by Suzuki-Miyaura coupling because of the instability of the corresponding boronic acids. A strategy to prepare and use *in situ* or as isolated material for cross coupling the pinacolboronate esters of unstable boronic acids has been developed. These pinacol boronates are synthesized using iridium-catalyzed C-H borylation, a direct and mild method for borylation, and are stable

indefinitely in isolated form on the benchtop. The corresponding boronic acids require cold, anaerobic storage. These boronate esters can also be used *in situ* for Suzuki coupling with aryl halides with easily accessible palladium catalysts in a one-pot procedure. Mechanistic studies revealed the features of the pinacolboronates that enable these cross couplings to occur in high yields. Protodeborylation of the pinacol boronate is slow, and the transmetallation of the pinacol boronate with an intermediate palladium hydroxide complex occurs rapidly without generation of the boronic acid. This C-H borylation and cross coupling sequence can be conducted on small or large scale and does not require the use of a glovebox. Because of the importance of these substructures, this methodology should find many applications.

In a third study focused on iridium-catalyzed C-H borylation, a method for site-selective borylation of nitrogen-containing heterocycles was developed. Selective methods for the functionalization of indoles and other nitrogen heterocycles would provide access to the core structures of many natural products and pharmaceuticals. Although there are many methods and strategies for the synthesis of substituted indoles or functionalization of the azole ring, strategies for the selective functionalization of the benzo-fused portion of the indole skeleton, particularly the 7-position, are less common. We report a one-pot, iridium-catalyzed, silyl-directed C−H borylation of indoles at the 7-position. This process occurs in high yield with a variety of substituted indoles, and conversions of the 7-borylindole products to 7-aryl-, 7-cinnamyl-, and 7-haloindoles are demonstrated. The Ir-catalyzed, silyl-directed C−H borylation also occurs with several other nitrogen heterocycles, including carbazole, phenothiazines, and tetrahydroquinoline.

The utility of this methodology is highlighted by the one-pot synthesis of a member of the pyrrolophenanthridone class of alkaloid natural products.

In another set of studies, a new approach to the use of high-throughput, multidimensional screening of transition metal catalysts and organic substrates was developed. Although high-throughput methods for catalyst discovery that would mirror related approaches for the discovery of medicinally active compounds have been the focus of much attention over the past fifteen years, these methods have not been sufficiently general or accessible to typical synthetic laboratories to be adopted widely. A method to evaluate a broad range of catalysts for potential coupling reactions using simple laboratory equipment has been developed. Specifically, an array of catalysts and ligands with a diverse mixture of substrates was screened, and then mass spectrometry was utilized to identify coupling products that by design exceed the mass of any single substrate. Using this method, we have discovered a copper catalyzed alkyne hydroamination reaction and two nickel-catalyzed hydroarylation reactions, all displaying excellent functional group tolerance.

To My Parents

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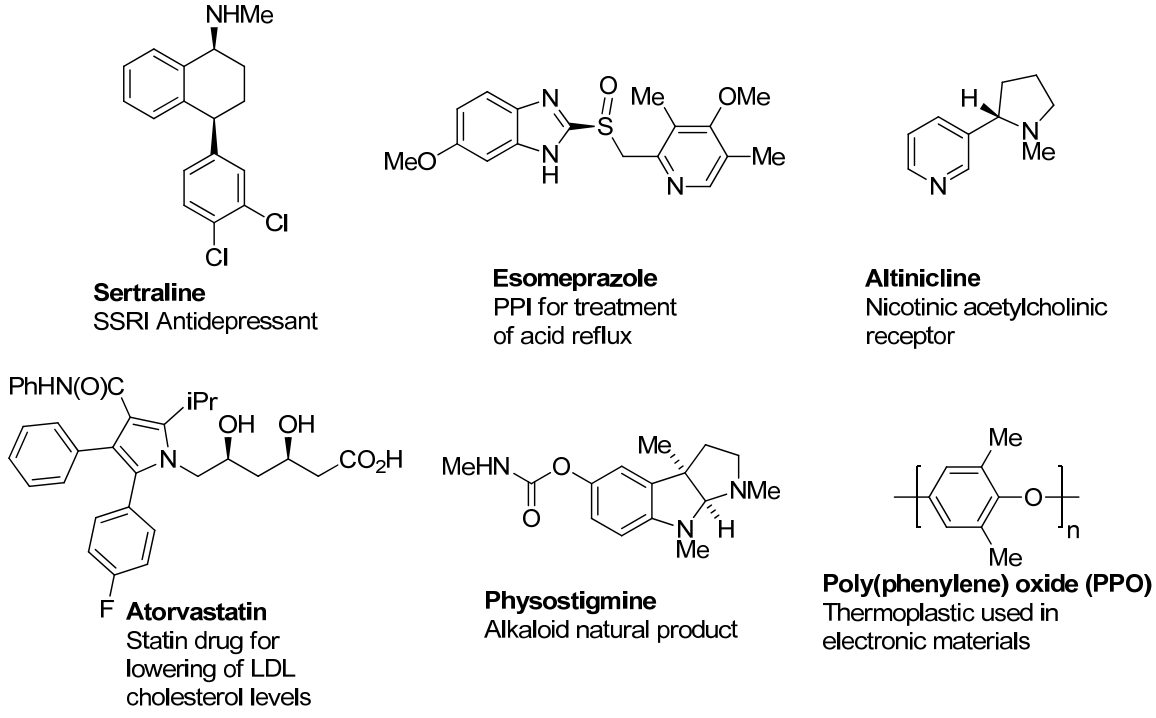
Chapter 1. Overview of Methods for the Control of Site-Selectivity in Transition Metal-Catalyzed Functionalization of Aromatic and Heteroaromatic C-H Bonds

1.1 Introduction

The synthesis of organic molecules relies upon the transformation of inherently reactive functional groups, such as carbonyl groups, halogens, or alcohols, into the desired structural features of a target molecule. The development of new methodology, or new ways to transform these functional groups, in synthetic organic chemistry has the potential to address many crucial challenges in medicine, energy production and materials science. New synthetic methodology can present approaches for the synthesis of fundamentally new molecules, or new methods can enable a more direct to construct a desired compound, generally by enabling the synthesis in higher yield, fewer synthetic operations, higher levels of site-, chemo- or stereoselectivity, or with generation of fewer wasteful byproducts.[1-3] One promising area that has sought to address these challenges of more efficient and streamlines synthesis is transition metal-catalyzed C-H functionalization reactions. While C-H bonds are generally not considered to be reactive functional groups, their ubiquity in many types of molecules makes them an attractive target for synthetic manipulation. Synthetic methods involving C-H functionalization convert C-H bonds into C-C, C-N, C-O or other types of C-heteroatom bonds. While there are many approaches to C-H functionalization, many of the most useful methods rely upon transition metal catalysts. The most attractive aspect of C-H functionalization in the context of complex molecule synthesis is the potential for these methods to decrease the length or efficiency of synthetic sequences. In addition, the ability to introduce a diverse set of functionality by direct C-H functionalization can allow for

rapid synthesis of a diverse set of structures from a simple starting material, which is often desirable in the context of medicinal chemistry.

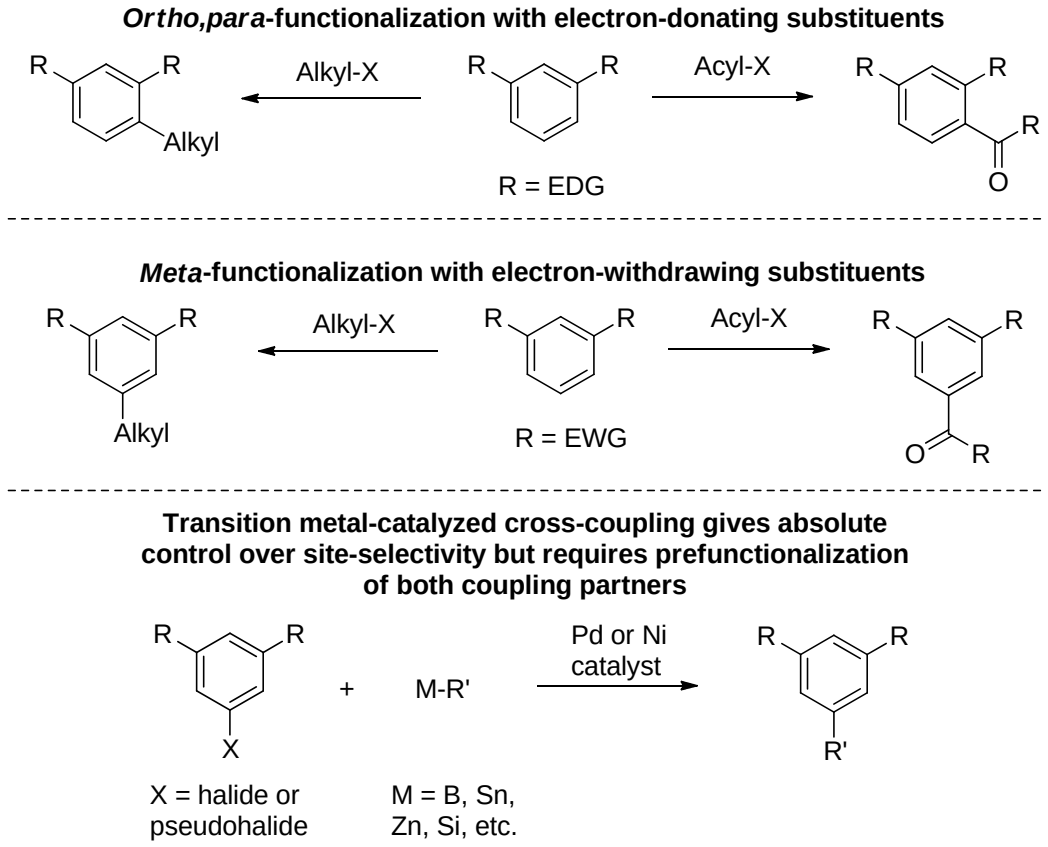
Because arenes and heteroarenes constitute important structures in molecules with a variety of functions, methods for the functionalization of arenes and heteroarenes, and more specifically of aromatic and heteroaromatic C-H bonds, have tremendous potential to improve approaches to the synthesis of various complex molecules. Arenes and heteroarenes form core scaffolds in pharmaceutical agents, natural products with various types of biological activity, and functional polymeric materials (Scheme 1).



Scheme 1. Pharmaceutical agents, natural products and functional polymers with arenes and heteroarenes as core structures

One of the oldest and most commonly utilized methods for the functionalization of arenes is electrophilic aromatic substitution. Electrophilic aromatic substitution, or Friedel-Crafts reactions, involves the reaction of a nucleophilic arene with an alkyl halide

or acyl halide to form an alkylated or acylated arene product. The site-selectivity of these transformations is controlled by the electronic properties of the arene (Scheme 2). In general, electron-donating substituents lead to functionalization at the *ortho/para* positions. Electron-withdrawing substituents direct functionalization to the *meta* position of the aromatic ring. Another strategy to control the site-selectivity of arene functionalization is through Pd- or Ni-catalyzed cross-coupling reactions. In these reactions, an aromatic halide or pseudohalide is coupled with an organometallic reagent, such as a Mg, Zn, Sn, B or Si compound. While these reactions have proven to be invaluable in organic synthesis and have become some of the most highly utilized methods for the formation of C-C and C-X bonds, prefunctionalization of both the electrophilic and nucleophilic coupling partners is required.



Scheme 2. Friedel-Crafts and transition metal-catalyzed cross-coupling approaches to arene functionalization

1.2 Transition Metal-Catalyzed Functionalization of Aromatic C-H Bonds

Another potential strategy to address the challenge of arene and heteroarenes functionalization is through the use of transition metal catalysts. Two primary challenges exist in developing effective catalysts for C-H functionalization of aromatic C-H bonds. The first challenge is catalyst activity. Because C-H bonds are generally inert, catalysts must be specifically designed to both cleave the C-H bond and to convert the C-H bond into a C-C or C-heteroatom bond. To this end, many studies have described the discovery and development of transition metal complexes that activate aromatic, heteroaromatic and aliphatic C-H bonds.[4-7] The second challenge is to control the site-selectivity of C-H

functionalization. Because C-H bonds are ubiquitous in organic structures, to be synthetically useful, a catalyst must be able to differentiate between the many C-H bonds in a molecule and only functionalize a single C-H bond to provide optimal catalytic activity and selectivity. Several of the strategies for the control of site-selectivity for transition metal-catalyzed aromatic C-H activation will be discussed (*vide infra*). These strategies can be placed into the following three categories:

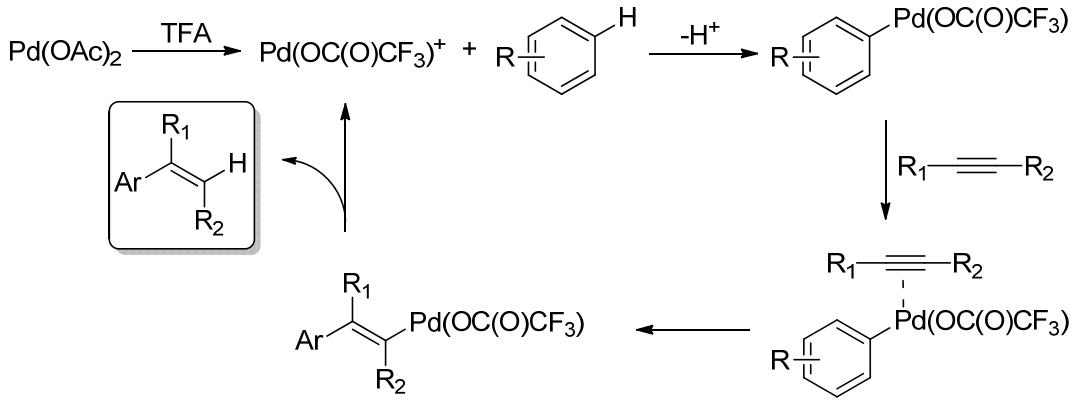
1) Site-selectivity control by the electronic properties of the arene
2) Site-selectivity control by a substituent of the arene acting as a directing group
3) Site-selectivity controlled by the steric properties of the arene

In addition to C-H functionalization of arene C-H bonds, many synthetic methods for the site-selective functionalization of heteroaromatic C-H bonds have also been developed. Because heteroaromatic structures are particularly important in pharmaceuticals and medicinal chemistry, these methods have the potential to find widespread practical utility. In addition, for many classes of heteroarenes, the presence of a heteroatom(s) in an aromatic molecule often provides new opportunities for the control of site-selectivity in transition metal-catalyzed C-H functionalization (*vide infra*).

1.2.1 Functionalization of Aromatic C-H Bonds by Electrophilic Metal Species

One approach to the control of the site-selectivity of transition-metal catalyzed functionalization of aromatic C-H bonds is through the use of electrophilic metal species.[8] The site-selectivity of this type of transformation is similar to that of conventional electrophilic aromatic substitution with alkyl or acyl halides in conjunction with a Lewis acid. Metallation by electrophilic metal species occurs at the most electron-rich and most nucleophilic C-H bond of an arene. Following C-H bond cleavage, reaction

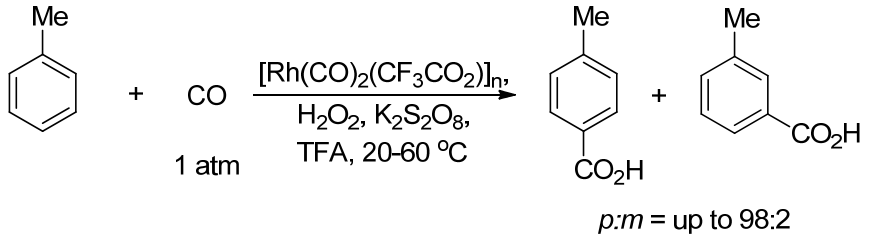
with an alkene or alkyne provides a reduced product from hydroarylation of the unsaturated molecule.[9] Common catalysts for these transformations include $Pd(OAc)_2$ and $Pt(OAc)_2$ in combination with trifluoroacetic acid (TFA). Mechanistic proposals for the Pd-catalyzed process suggest reaction of $Pd(OAc)_2$ with TFA forms a highly electrophilic, unsaturated, cationic $Pd(TFA)^+$ species that undergoes reaction with an aromatic C-H bond (Scheme 3). Alkyne coordination and insertion into the aryl-Pd(II) trifluoroacetate complex followed by protonation of the carbon-palladium bond releases the hydroarylation product and regenerates the active catalyst. Electrophilic palladium catalysts have also been utilized for *para*-selective, oxidative, C-H/C-H biaryl formation with an *N*-fluorosulfonimide as the oxidant.[10] Electrophilic Cu(III) catalysts, formed by reaction of Cu(II) precatalysts with aryliodonium salts, have been utilized for *para*-selective arylation of aniline and phenol derivatives.[11]



Scheme 3. Mechanism of electrophilic Pd-catalyzed hydroarylation of alkynes

Other electrophilic metal species have also been utilized in catalytic functionalization of aromatic C-H bonds. Electrophilic Rh(III) complexes have been utilized for site-selective carbonylation and carboxylation of aromatic C-H bonds (Scheme 4).[12] The active catalyst for the carbonylation/carboxylation transformation is proposed to be a Rh(III)-TFA complex that catalyzes C-H cleavage at the most electron-

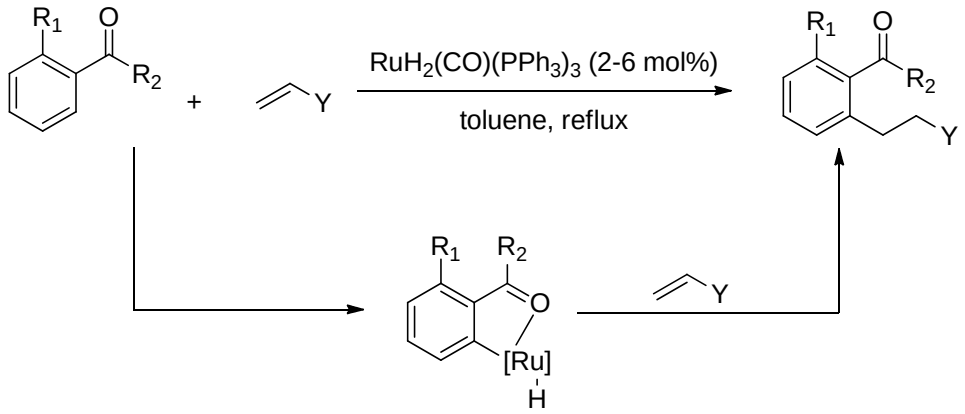
rich position of the arene. Rh-catalyzed carboxylation of toluene furnishes high selectivity for *p*-toluic acid. Oxidative olefination of simple arenes with Ru complexes has also been reported, but modest site-selectivities were observed. Rate acceleration was observed with more electron-rich arenes, indicating the intermediacy of an electrophilic Ru center.[13]



Scheme 4. Rhodium-catalyzed carboxylation of aromatic C-H bonds

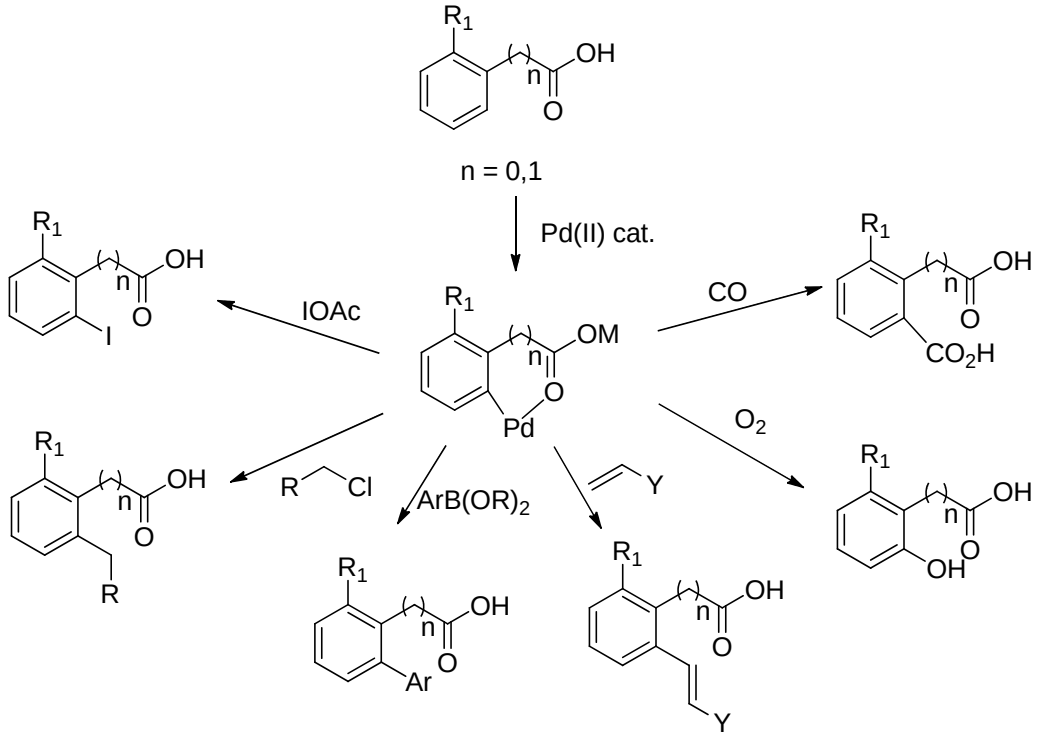
1.2.2 Control of Site-Selectivity of Aromatic C-H Bond Functionalization by Chelating Directing Groups

In addition to site-selectivity determined by the electronic properties of the arene, the site-selectivity of aromatic C-H functionalization can be controlled by a directing group. In this approach, the substrate contains a functional group that is capable of serving as a temporary ancillary ligand and to bring the transition metal catalyst in proximity to a single C-H bond within the molecule. One of the first examples of the use of a directing group for aromatic C-H functionalization was reported by Murai. In this seminal report, Murai and co-workers observed ortho-alkylation of aromatic ketones with olefins catalyzed by $RuH_2(CO)(PPh_3)_3$ (Scheme 5).[14-15] High yields were generally observed, and a variety of olefins, including olefins bearing alkyl and aryl groups, in addition to vinyl and allyl silanes, could be utilized. Since this initial report, a variety of oxygen-directed, ortho-selective C-H functionalization methods for the construction of C-C and C-X bonds have been reported.[16]



Scheme 5. Ruthenium-catalyzed, ketone-directed *ortho*-alkylation via aromatic C-H activation

Following the development of ketone-directed *ortho*-alkylation by Murai, other methods to utilize oxygen-based directing groups have been developed. In several methods, carboxylate directing groups in benzoic acids or phenylacetic acids in conjunction with Pd(II) catalysts and an oxidant direct formation of C-C or C-X bonds at the *ortho*-position (Scheme 6). These methods rely upon directed cyclometallation at the *ortho* position, followed by functionalization triggered by reaction with various coupling partners.[17] In several of these transformations, Pd(0) is generated from reductive elimination during formation of the functionalized product. Therefore, to regenerate the active Pd(II) species, an external oxidant is required. This oxidant is often a silver salt of p-benzoquinone, but in some cases O_2 gas or air can be used as a more economic and environmentally benign oxidant.

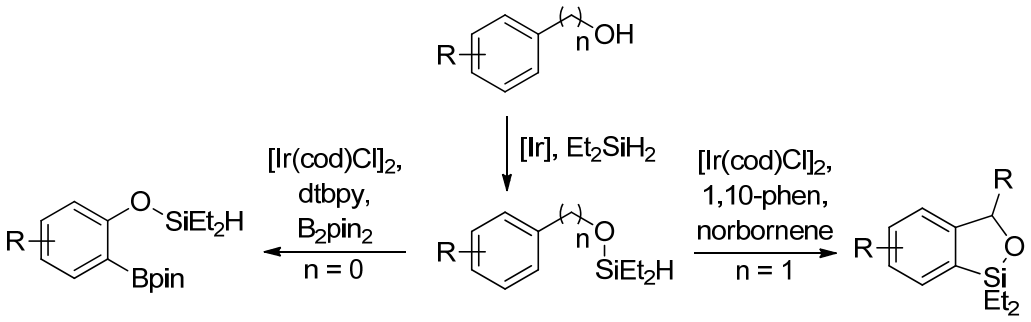


Scheme 6. Pd-catalyzed, carboxylate-directed *ortho*-selective functionalization of aromatic C-H bonds

Along with carboxylic acids, alcohols and amides have been used to direct Pd(II) catalyzed functionalization to *ortho* aromatic C-H bonds. These methods allow for *ortho*-selective amination,[18] fluorination,[19] etherification,[20] borylation,[21] and alkenylation.[22] Along with carboxylic acids, amides and alcohols, esters have been utilized as an *ortho* directing group. A silica-supported iridium catalyst catalyzed the *ortho* borylation of aryl and heteroaryl esters, amides and ethers with B_2pin_2 as the boron source.[23-24]

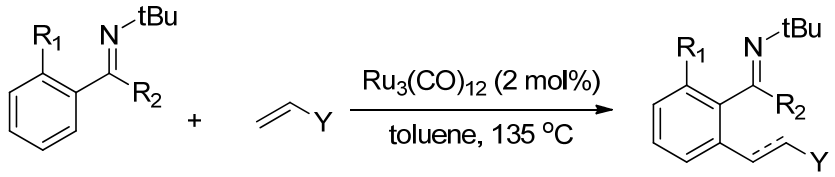
While oxygen-containing functionality can be used directly as a steering group to control the site-selectivity of C-H functionalization, covalent modification of alcohols can also be used to introduce other directing groups. This approach has been successfully applied to the *ortho*-selective borylation[25] and silylation[26] of aromatic C-H bonds (Scheme 7). In both of these approaches, initial iridium-catalyzed, dehydrogenative

silylation of an alcohol with diethylsilane forms a hydrosilyl ether. In the case of *ortho*-borylation, this hydrosilyl ether directs borylation with B_2pin_2 at the *ortho* C-H bond. In the case of *ortho*-silylation, after formation of the silyl ether, Ir/phenanthroline-catalyzed dehydrogenative arene silylation occurs, to form a benzosilole as the product.



Scheme 7. Hydrosilyl-directed, iridium-catalyzed *ortho* borylation and silylation of aromatic C-H bonds

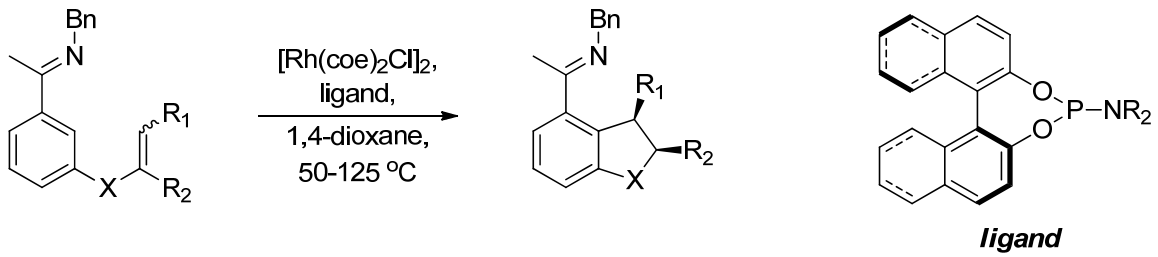
In addition to oxygen-directed *ortho*-functionalization of aromatic C-H bonds, several methods for nitrogen-directed *ortho*-functionalization have been developed. Early examples of nitrogen-based directing groups demonstrated similar methods to the ketone-directed alkylation pioneered by Murai. Rhodium[27] and ruthenium[28] complexes *catalyze* ortho-functionalization with pyridyl groups, imidates or imines as the internal, directing ligand (Scheme 8). In the cases of the ruthenium-catalyzed *ortho*-functionalization of imidates and imines, a minor amount of alkenylation product is observed, presumably from fast β-hydride elimination relative to C-H reductive elimination. Ru-catalyzed *ortho*-acylation can be performed by coupling of *ortho* C-H bonds with CO gas and an olefin.[29-30]



Scheme 8. Ruthenium-catalyzed, imine-directed *ortho*-alkylation of aromatic C-H bonds\

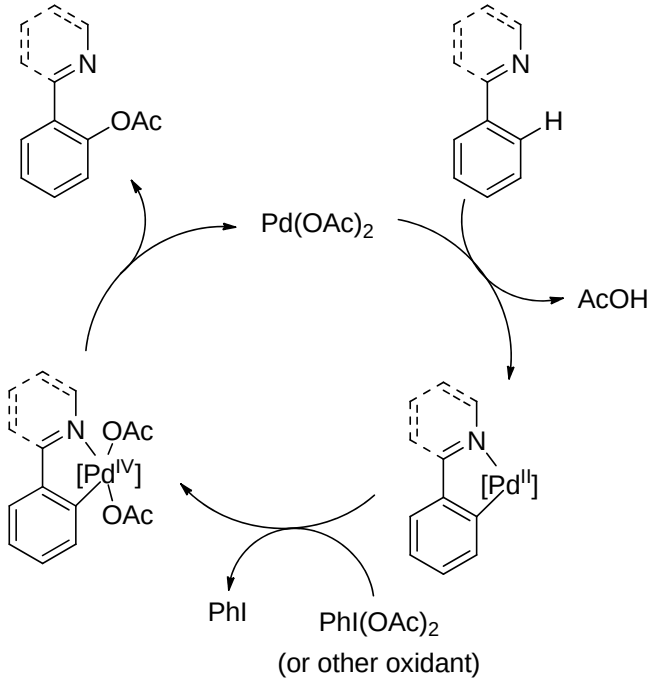
Nitrogen-directed arylation of *ortho* aromatic C-H bonds has also been accomplished with rhodium and ruthenium catalysts. Arylation of 2-phenylpyridine derivatives with $Rh(PPh_3)_3Cl$ as the catalyst and Ar_4Sn as the source of the aryl group has been demonstrated. A potentially more useful ruthenium-catalyzed *ortho*-arylation of 2-phenylpyridine derivatives[31] and aryl imines[32] was reported by Oi and coworkers with aryl halides. The proposed mechanism for these transformations entails initial oxidative addition of the aryl halide by a Ru(II)-phosphine complex, followed by electrophilic attack of the resulting Ru(IV) aryl halide complex at the *ortho* position after coordination to the nitrogen directing group. Elimination of HX forms a nitrogen-coordinated diaryl complex, which undergoes reductive elimination to form the biaryl product and regenerate the Ru(II) species.

Enantioselective, rhodium-catalyzed C-H activation/alkylation methods have also been developed. Bergman, Ellman and co-workers have developed chiral rhodium catalysts for imine-directed C-H functionalization followed by olefin insertion to form stereocenters in an enantioselective fashion (Scheme 9). Use of chiral, non-racemic phosphoramidite ligand in combination with a Rh(I) precatalysts enables enantioselective synthesis of substituted indanes and dihydrobenzofurans with high levels of enantioselectivity and diastereoselectivity.[33-34]



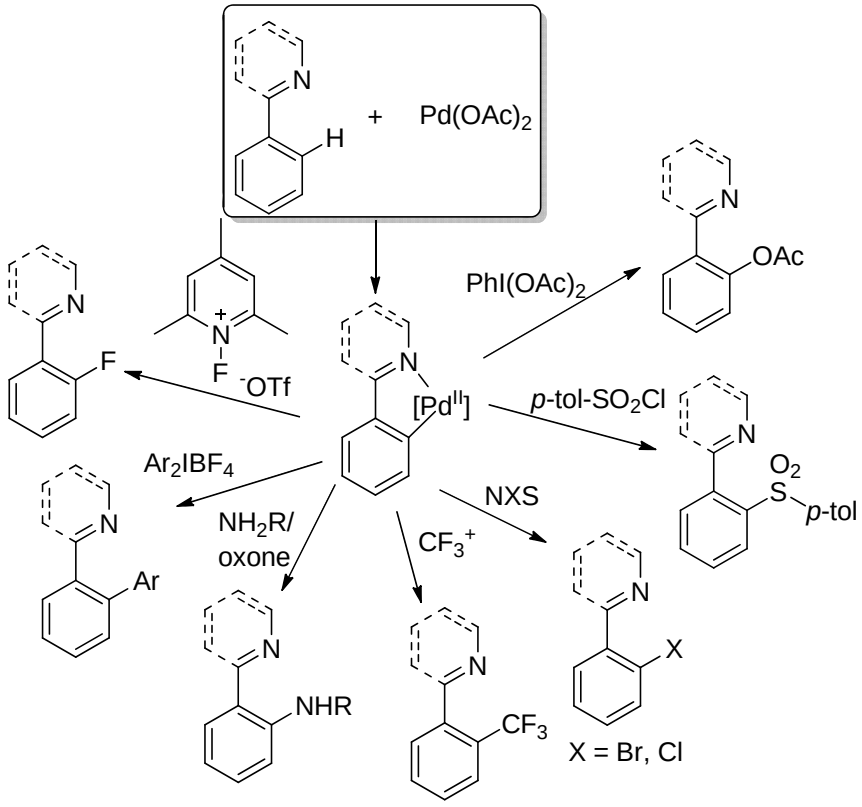
Scheme 9. Enantioselective, rhodium-catalyzed alkylation via nitrogen-directed aromatic C-H bond activation

In addition to ruthenium and rhodium catalysts, palladium complexes have been utilized for nitrogen-directed, *ortho*-selective functionalization of aromatic C-H bonds.[35] The use of palladium catalysts for nitrogen-directed C-H functionalization has allowed for the introduction of more diverse functionality, including the formation of C-C, C-O, C-N, C-S and C-X (X=halogen) bonds. Palladium catalysts have been particularly effective for this type of transformation because they undergo reaction with a variety of reagents for functionalization, and palladium complexes readily undergo cyclometallation reactions with *ortho* C-H bonds with a variety of directing groups. A general mechanism for this transformation is shown in Scheme 10. In general, a Pd-carboxylate salt undergoes initial cyclometallation with an *ortho*, aromatic C-H bond, facilitated by a nitrogen directing group, with concomitant loss of acid. Following metallacycle formation, the Pd(II) center undergoes oxidation form a Pd(IV) (or Pd(III))[36] intermediate with transfer of the transferable organic group. Following oxidation, this high-valent palladium intermediate undergoes reductive elimination to produce the functionalized product and regenerate Pd(II).



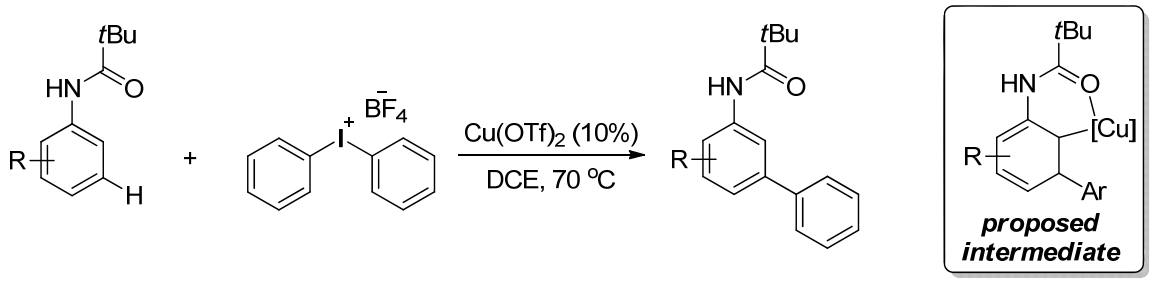
Scheme 10. General mechanism for Pd-catalyzed *ortho*-selective functionalization with nitrogen directing groups

Following initial development of Pd-catalyzed, *ortho*-selective oxygenation of 2-phenylpyridine derivatives,[37] a variety of methods for Pd-catalyzed, nitrogen-directed arene C-H functionalization have been developed (Scheme 11).[35] Methods for oxygenation, sulfonylation, halogenation, trifluoromethylation, arylation and amination have been developed. In addition, a variety of directing groups, including pyridyl groups, pyrazines, pyrimidines, pyrazoles, imines, oxazolines, oximes and amides can be utilized. Along with aromatic C-H functionalization, many of these methods have been extended to allow for similar, directed functionalization of aliphatic C-H bonds.



Scheme 11. Diversity of bond constructions via nitrogen-directed functionalization of *ortho* C-H bonds

Directing groups can also be utilized to enable *meta*-selective arene functionalization. An example of this class of arene functionalization utilizes highly electrophilic copper catalysts to perform *meta*-selective arylation of aryl amides (Scheme 12).[38] In this methodology, pivaloyl anilines undergo arylation with aryliodonium salts in the presence of a catalytic amount of $Cu(OTf)_2$. the meta selectivity is proposed to arise via a Heck-like intermediate that directs the Cu center to the *ortho* position by coordination to the anilide and delivers the aryl group to the *meta* position.[39] In addition to *meta*-arylation of anilides, this methodology has been extended to *meta*-selective arylation of phenylacetic acid derivatives.[40] Ruthenium-catalyzed *meta*-selective sulfonylation of 2-phenylpyridine derivatives has also been reported.[41]

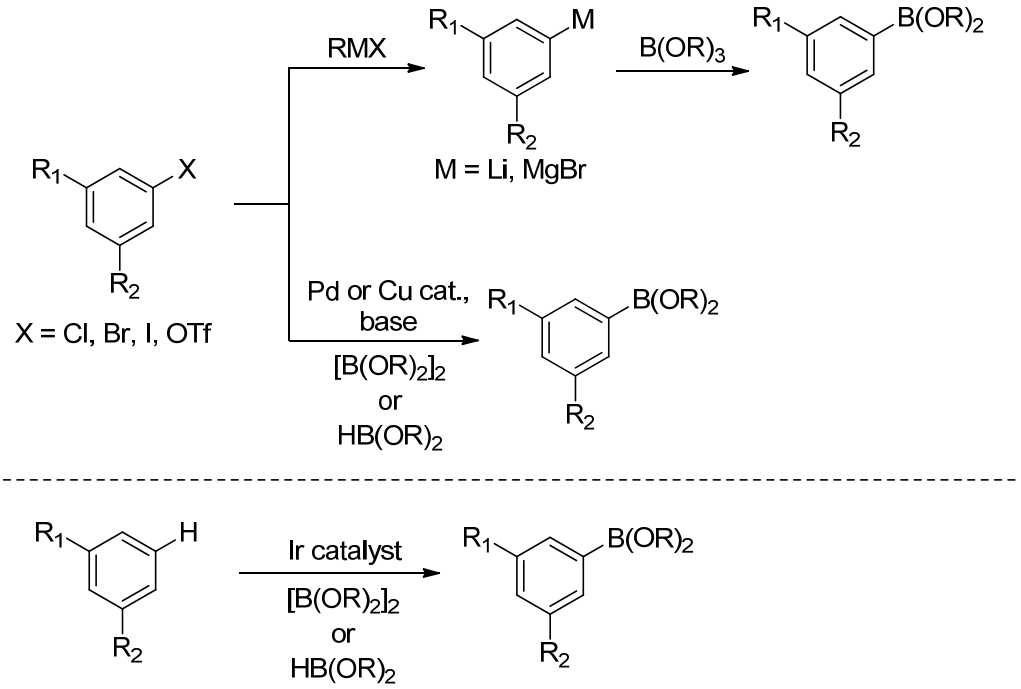


Scheme 12. Copper-catalyzed *meta*-arylation of aryl amides with aryliodonium salts

1.2.3 Control of Site-Selectivity of Aromatic C-H Bond Functionalization by the Steric Properties of the Arene

Another general approach to the control of site-selectivity of aromatic C-H functionalization is through steric effects. These methods enable aromatic C-H bond activation with complementary regioselectivity to those methods which require a directing group. Several approaches for the selective functionalization of the most sterically-accessible C-H bond of an arene have been developed. Directed C-H functionalization is inherently limited by the presence of the directing group, which in the context of synthetic applications either must be a structural element of the desired target, or requires installation and removal following functionalization. While some directing groups are easily removed,[42-43] other groups such as pyridyl groups, are not easily removed, thus limiting the synthetic applications of these directing groups in the context of organic synthesis. One of the first and most well-developed methods for arene functionalization with the site-selectivity controlled by steric effects is transition metal-catalyzed borylation of aromatic C-H bonds.[44] In the borylation of arenes, C-H functionalization generally occurs at the least hindered C-H bond of an arene. In addition to forming functionalized arenes with complementary site-selectivity to other methods, this method forms an aryl boronate by direct activation of a C-H bond, alleviating the

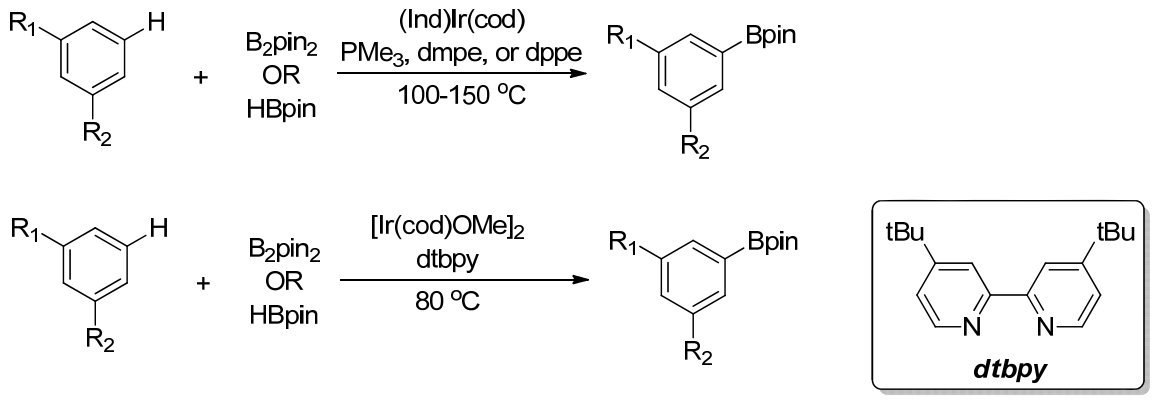
need for a pre-functionalized precursor, generally an aryl halide (Scheme 13). Two common methods for the preparation of aryl boronates from aryl halides are metallation of aryl halides with magnesium or lithium reagents followed by quenching with a borate electrophile, and a more mild Pd-catalyzed[45] or Cu-catalyzed[46] method for borylation of aryl halides with diboron or borane reagents. The direct borylation of C-H bonds provides a more direct borylation method which does not rely upon the synthesis of an aryl halide.



Scheme 13. Approaches to the synthesis of aryl boronates from aryl halides and aromatic C-H bonds

Borylation of aromatic C-H bonds is catalyzed by iridium[47] and rhodium[48] complexes, with iridium catalysts being more widely utilized. Two classes of catalysts for the iridium-catalyzed borylation of aromatic C-H bonds with bis(pinacolato)diboron (B_2pin_2) have been developed (Scheme 14). One class of catalysts utilizes an Ir(I) precatalyst in combination with monodentate or bidentate phosphine ligands.[49] The second, more active catalyst class utilizes and Ir(I) precatalyst along with 4,4'-di-*tert*-

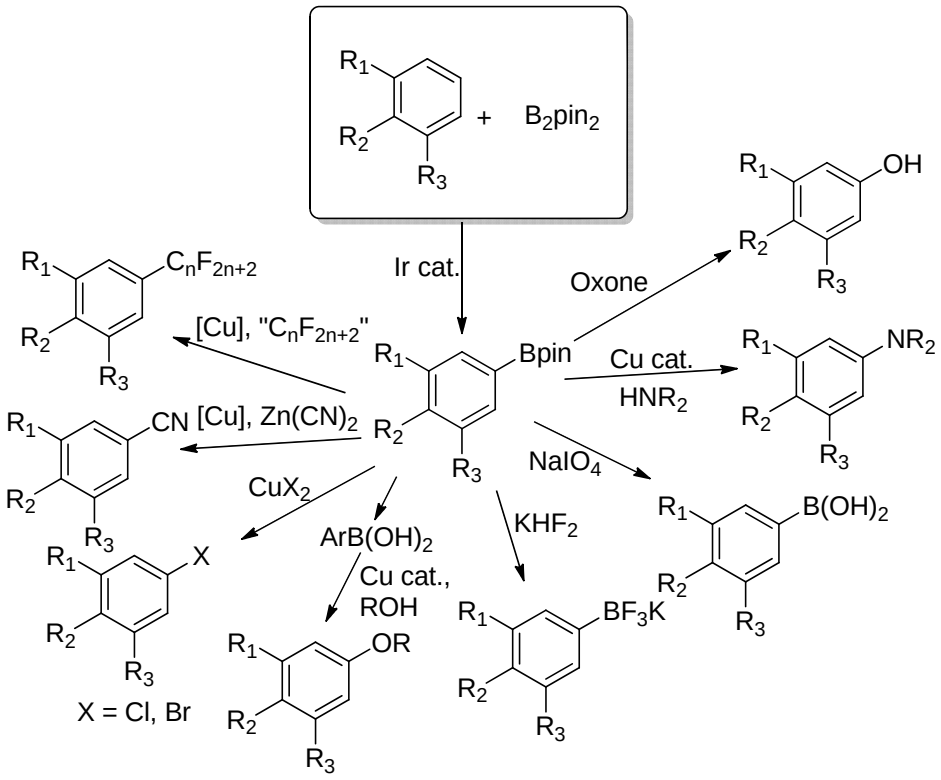
butylbipyridine (dtbpy) as the ancillary ligand.[50] Both catalysts can achieve high turnover numbers and maintain the sterically-controlled site-selectivity, providing borylation at the least hindered C-H bond of simple arenes. In addition to catalyst and ligand structure, the structure of the diboron compound imparts a significant effect on the borylation. The borylation occurs in higher yield and with higher turnover number when a more sterically hindered and more electron rich group is placed on the boron atoms of the diboron compound.[51] Therefore, pinacolate boron esters provides higher yields in the iridium-catalyzed C-H borylation reaction than does catecholate boron esters. In addition to the use of alkoxide substituents on the boron atom, the iridium-catalyzed C-H borylation can be conducted with HBDan (Dan = 1,8-diaminonaphthalene).[52] Arenes containing the BDan group are useful in iterative Suzuki-Miyaura cross-coupling.[53]



Scheme 14. Two classes of catalysts for iridium-catalyzed borylation of arenes

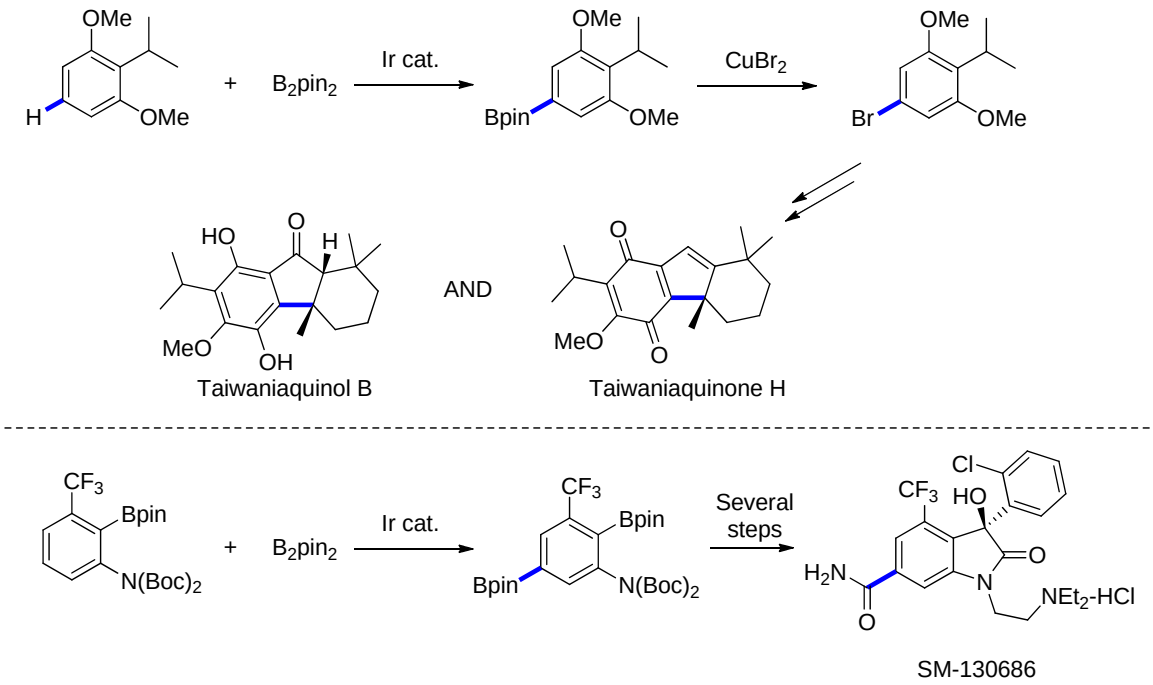
While the *meta*-selectivity of the iridium catalyzed C-H borylation provides a method to access arenes with substitution patterns that would difficult to synthesize by other methods, the resulting boronate esters are of greater utility if they can be functionalized into a variety of other compounds to allow for the synthesis of several classes of substituted arenes.[54] Apart from Suzuki-Miyaura coupling with aryl electrophiles, several methods for the introduction of diverse functionality by

functionalization of an aryl pinacol boronate ester formed by C-H borylation have been developed, generally in a one-pot fashion, which allows for increased synthetic efficiency (Scheme 15). 3,5-disubstituted phenols can be synthesized by oxidation of a pinacol boronate ester with Oxone.[55] In an extension of this methodology, 3-aminophenols can by formed by borylation of a 3-substituted aryl halide, followed by Pd-catalyzed amination and oxidation of the aryl boronate.[56] Chan-Lam coupling of the crude aryl boronate ester to form aryl amines[57] and aryl nitriles[58] occurs with readily available Cu catalysts. Aryl ethers can also by formed by hydrolysis of the aryl boronate ester to the boronic acid, followed by Cu-catalyzed coupling with an alcohol.[57] Cu-catalyzed halogenation with CuX_2 (X = Cl, Br) provides access to *meta*-substituted aryl halides, which are difficult to synthesize by conventional electrophilic aromatic substitution reactions.[59] *Meta*-substituted aryl fluorides were also synthesized by initial boronic acid formation by hydrolysis, followed by silver-catalyzed fluorination with an electrophilic fluorination reagent.[60] *Meta*-substituted perfluoroalkyl arenes were formed by perfluoroalkylation of the pinacol boronate ester formed from C-H borylation with Cu-perfluoroalkyl complexes under oxidative conditions.[61-62] Boronate esters formed in situ by Ir-catalyzed C-H borylation can be used for Rh-catalyzed conjugate addition to α,β–unsaturated ketones to form β-arylketones.[63] Finally, other organoboron compounds can be synthesized from the crude pinacol boronates, including aryl boronic acids, by acidic hydrolysis in the presence of $NaIO_4$, and the potassium trifluoroborate salt by treatment of the pinacol boronate with aqueous KHF_2.[64] The synthetic diversity that can be accomplished with the aromatic C-H borylation platform makes this transformation a useful method in organic synthesis.



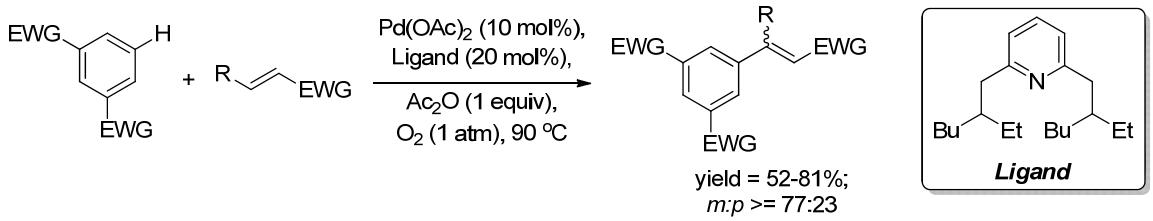
Scheme 15. Functionalization of aryl boronate esters formed by *meta*-selective, iridium-catalyzed C-H borylation

In addition to being used for the synthesis of simple, substituted arenes, iridium-catalyzed C-H borylation has been used in the total synthesis of complex small molecules (Scheme 16).[54] *Meta*-selective borylation followed by halogenation of the resulting pinacol boronate was utilized by Hartwig and co-workers in the synthesis of Taiwaniaquinol B and Taiwaniaquinone H.[65] *Meta*-selective borylation and conversion of the aryl pinacol boronate ester to a primary amide was utilized by Shibasaki and co-workers in the synthesis of SM-130686, a potent human growth secretagogue (Scheme 15).[66] These applications illustrate the potential for the use of iridium-catalyzed C-H borylation for the construction of complex targets.



Scheme 16. Use of C-H borylation in the total synthesis of natural products and pharmaceutical candidates

In addition to iridium-catalyzed C-H borylation, there are other methods for functionalization of aromatic C-H bonds with the site-selectivity governed by the steric properties of the arene. One example was reported by Yu and co-workers.[67] This methodology describes the *meta*-selective olefination of electron-deficient arenes under aerobic, oxidative conditions (Scheme 17). The key to the development of the catalyst was the use of a bulky pyridine ligand, which enables selectivity for cleavage of the *meta* C-H bond. However, this method is limited to electron-deficient arenes and requires high catalyst loading. Other methods the *meta*-selective olefination[68] and arylation[69] of pyridines. These methods generally require large excess of the pyridine substrate, but nonetheless are potentially useful in the context of medicinal chemistry applications.



Scheme 17. *Meta*-selective, palladium-catalyzed olefination of electron-deficient arenes

1.3 Transition Metal-Catalyzed Functionalization of Heteroaromatic C-H Bonds

In addition to transition metal-catalyzed C-H functionalization of arenes, several methods have been developed for C-H activation of heteroaromatic C-H bonds. These methods can be divided into two categories based upon the heteroaromatic substrates:

1) Functionalization of C-H bonds in pyridines and pyridine derivatives
2) Functionalization of C-H bonds in azole rings

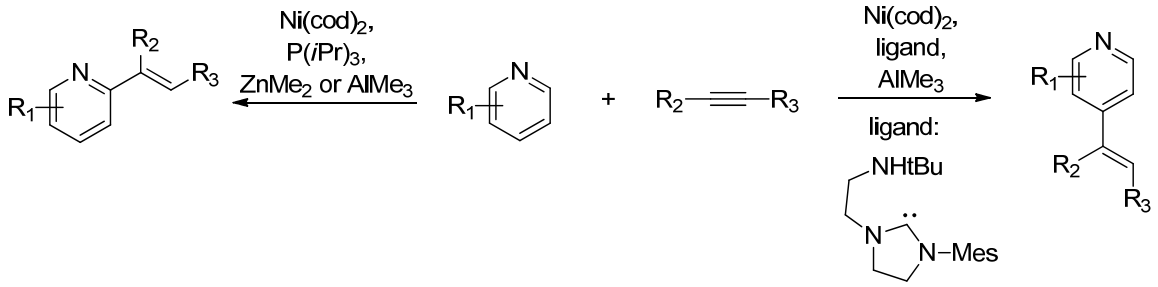
The site-selectivity of the C-H functionalization is generally controlled by the electronic properties of the C-H bonds in the heteroarenes, or by association or temporary binding of the heteroatom of the substrate with the metal center.

1.3.1 Transition Metal-Catalyzed Functionalization of C-H bonds in Pyridines and Pyridine Derivatives

Rhodium catalysts have been utilized for the direct alkylation and arylation of pyridines at the 2-position.[70] Bergman and Ellman have discovered rhodium catalysts for the selective alkylation of 2-substituted pyridines with olefins.[71] This transformation is catalyzed by the combination of a Rh(I) precatalyst and PCy_3-HCl as the ancillary ligand and a very high temperature is required to obtain a high yield. Use of the phosphonium salt of the ancillary ligand is crucial, presumably because the substoichiometric acid additive protonates the nitrogen atom of the pyridine, and this pyridinium salt undergoes

alkylation at the 2-position. This methodology has also been extended to Rh-catalyzed direct arylation at the 2-position of pyridines with aryl bromides.[72]

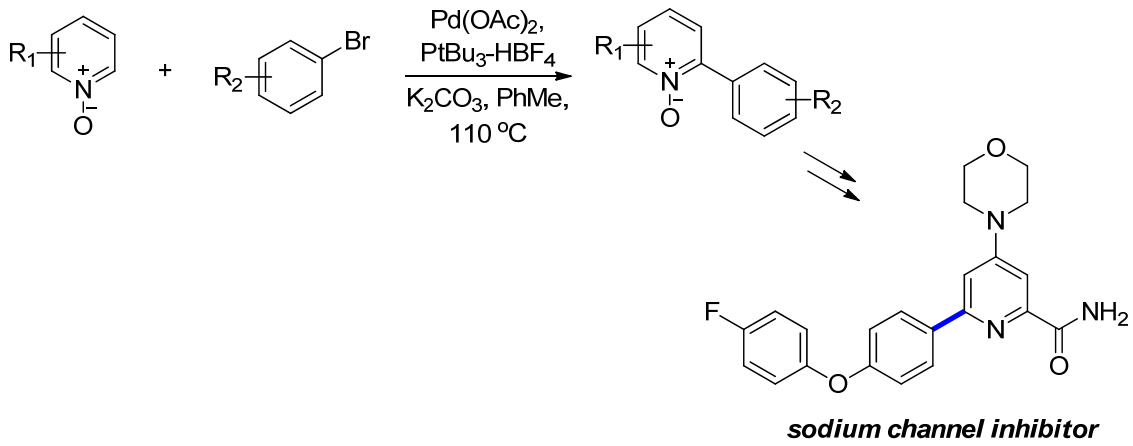
Nickel catalysts have also been utilized for the introduction of various functional groups at different sites of pyridines (Scheme 18). Nakao, Hiyama and co-workers have reported nickel catalysts for the alkenylation of pyridines at the 2-position in conjunction with a Lewis acid. In this methodology, reaction of a pyridine with an alkyne in the presence of a Ni-phosphine catalyst and $AlMe_3$ as the Lewis acid provides 2-alkenylpyridines in good yield and with high site-selectivity.[73] The site-selectivity of this transformation can be altered to give alkenylation at the 4-position of pyridine simply by substituting a bidentate NHC-amine ligand for the phosphine.[74] C-4- selective alkylation of pyridines with high site-selectivity has also been demonstrated by reaction of pyridines with alkenes in the presence of a Ni-NHC catalyst and an aluminum Lewis acid.[75]



Scheme 18. Nickel-catalyzed alkenylation of pyridines at the C-2 and C4 positions

Pyridine N-oxide has also been used as a heteroaromatic substrate for direct C-H functionalization at the 2-position (Scheme 19). Fagnou and co-workers have demonstrated that pyridine N-oxides can undergo direct arylation with aryl bromides catalyzed by the complex formed from the combination of $Pd(OAc)_2$ and P*t*Bu_3 in the presence of K_2CO_3 as the base.[76] Imidazole N-oxides, oxazole N-oxides, and thiazole N-oxides can also be utilized as substrates for arylation with aryl bromides, and this

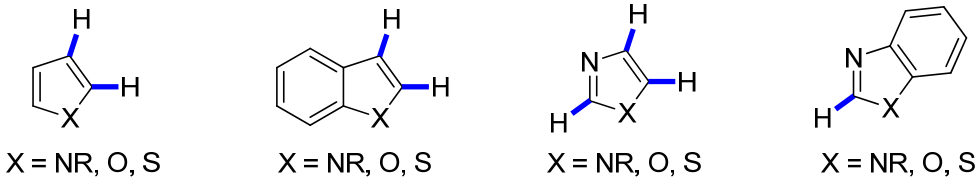
methodology has been utilized in the total synthesis of complex small molecules with biological activity.[77] This methodology has been extended to the oxidative direct arylation of pyridine N-oxides with olefins and arenes in the presence of $Pd(OAc)_2$ and Ag_2CO_3 as both the base and the oxidant.[78]



Scheme 19. Pd-catalyzed, direct arylation of pyridine N-oxides with aryl bromides

1.3.2 Transition Metal-Catalyzed Functionalization of C-H bonds in Azole Heterocycles

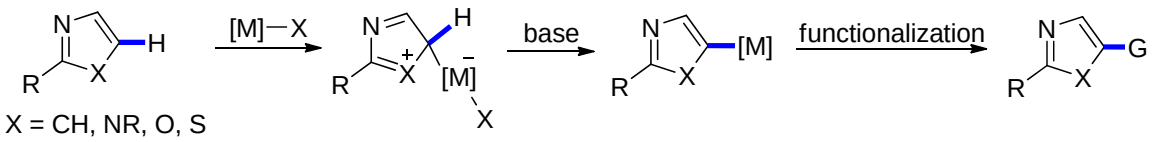
Due to their importance in natural product synthesis and medicinal chemistry, many synthetic methods have been developed for C-H activation of azole heterocycles. In general, azole heterocycles exhibit high reactivity towards transition metal-catalyzed C-H functionalization relative to simple arenes. In addition, the electronic properties of the various C-H bonds in an azole heterocycle allow for catalyst discrimination between the various C-H bonds and enable site-selective synthetic manipulation of these heteroarenes (Scheme 20). In more recent developments, catalyst design or other strategies have allowed for the development of transition metal complexes that can modify the site-selectivity from this inherent reactivity of azole C-H bonds.



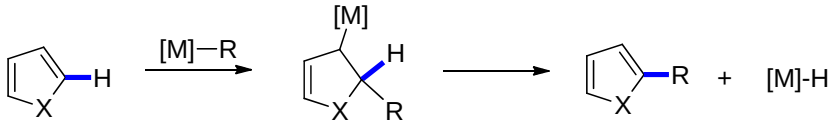
Scheme 20. Commonly reactive C-H bonds for transition metal-catalyzed C-H functionalization of azole rings

Many of the methods for C-H functionalization of azole C-H bonds can be placed into three different categories based upon mechanistic considerations (Scheme 21). The first type of transition metal-catalyzed azole functionalization is electrophilic aromatic substitution with an electron-deficient metal center. Nucleophilic attack of the azole on the metal center followed by deprotonation with an external base forms a heteroaryl metal complex. This complex then undergoes functionalization to form the product and regenerate the catalyst. In the second mechanism, the heteroarenes undergoes olefin insertion with a metal center, generally into a metal-carbon bond form a new bond and a dearomatized intermediate. β-hydride elimination then occurs to rearomatize and form the product and release a metal-hydride, which then regenerates the active catalyst. The final general mechanism for azole C-H functionalization involves deprotonation of the most acidic C-H bond of the azole ring followed by transmetallation with a transition metal species. This heteroaryl metal intermediate then undergoes functionalization to form the final product.

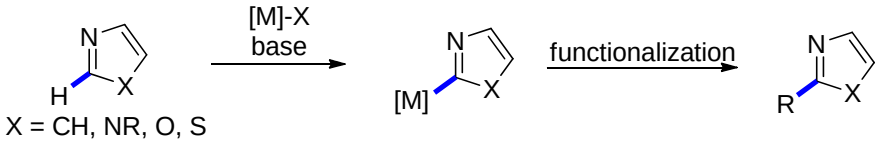
Mechanism 1: Electrophilic Aromatic Substitution



Mechanism 2: Heck-type Insertion/Elimination



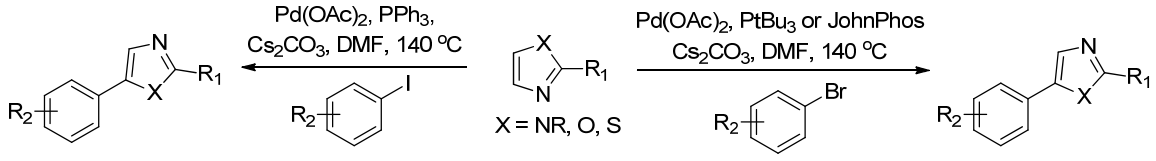
Mechanism 3: Cross-coupling via deprotonation and transmetallation



Scheme 21. General mechanisms for transition metal-catalyzed C-H functionalization of azole heterocycles

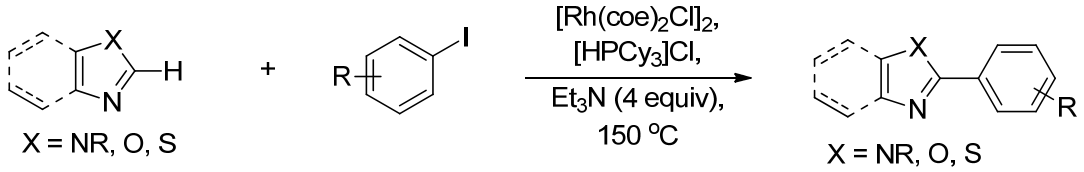
Direct C-H arylation is one of the most utilized methods for C-H functionalization of azole heterocycles.[16] Several palladium catalysts have been developed for intramolecular and intermolecular direct arylation of imidazoles, oxazoles and thiazoles (Scheme 22). Miura and co-workers demonstrated the arylation of 2-substituted N-alkylimidazoles, 2-substituted oxazoles, and 2-substituted thiazoles occurs at the 5-position with aryl iodides with palladium catalysts bearing simple arylphosphine ligands.[79] The scope of this reaction can be extended to aryl bromides with the use of P(*t*Bu)$_3$ or JohnPhos as the ancillary ligand. Direct arylation of these heterocycles with aryl bromides and pivalic acid as an additive has also been reported.[80] Copper additives have also been demonstrated to affect the reactivity and selectivity of these direct arylation reactions, and to act as a catalysts themselves in the absence of palladium

complexes.[81-83] In addition to direct arylation, Pd-catalyzed and Ni-catalyzed direct alkylation of oxazoles, benzoxazoles and benzothiazoles with primary alkyl halides has been reported.[84]



Scheme 22. Pd-catalyzed direct arylation of imidazoles, oxazoles and thiazoles with aryl bromides and aryl iodides

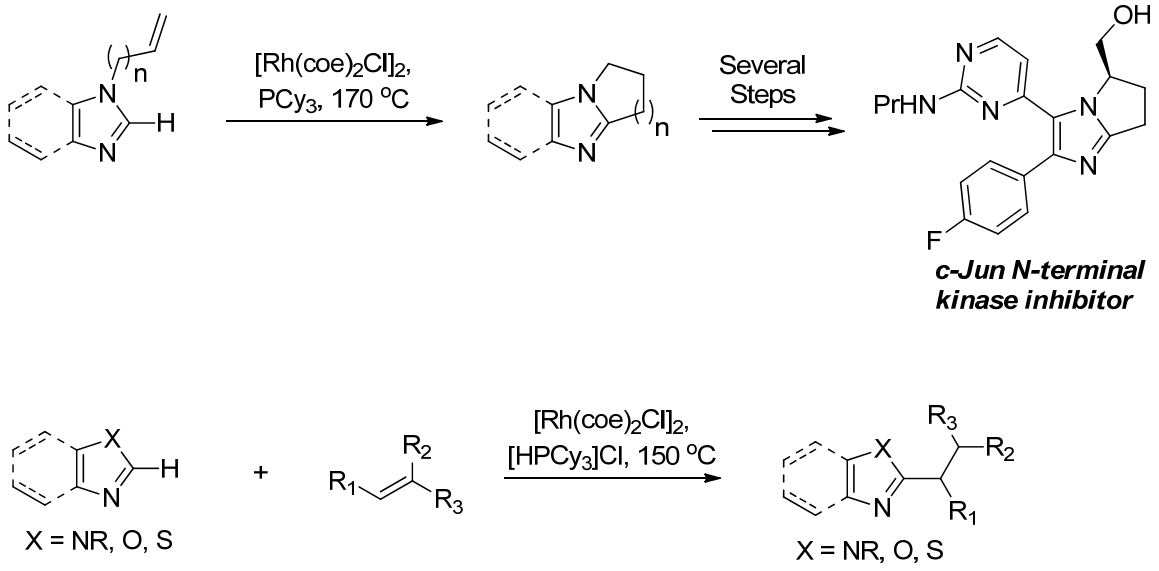
Rhodium catalysts have also been developed for the direct arylation and alkylation of (benz)imidazoles, (benz)oxazoles, and (benzo)thiazoles.[70] Arylation at the 2-position of azole heterocycles bearing two heteroatoms occurs with aryl iodides with Rh(I) catalysts bearing alkylphosphine ligands (Scheme 23). Although high temperatures are required, the scope is broad and the yield and site-selectivity of this transformation are generally high. This methodology was later extended to arylation with aryl bromides with a phosphepine ligand.[85-86]



Scheme 23. Rhodium-catalyzed direct C-H arylation of azole heteroarenes with aryl iodides

A similar method for rhodium-catalyzed alkylation of heteroaromatic C-H bonds with olefins has also been developed. An intramolecular alkylation of imidazoles and benzimidazoles was initially developed (Scheme 24).[87] Alkylation occurs at the 2-position with a Rh(I)-PCy_3 catalyst in good yield. Later developments extended this

methodology to intermolecular alkylation with terminal alkenes or cyclic internal alkenes.[88] Mechanistically, these arylation and alkylation reactions have been demonstrated to proceed via formation of an N-heterocyclic carbene complex following C-H activation by the Rh-phosphine catalyst, which then undergoes reaction with either an aryl halide or alkene to form the new C-C bond in the final product.[89]

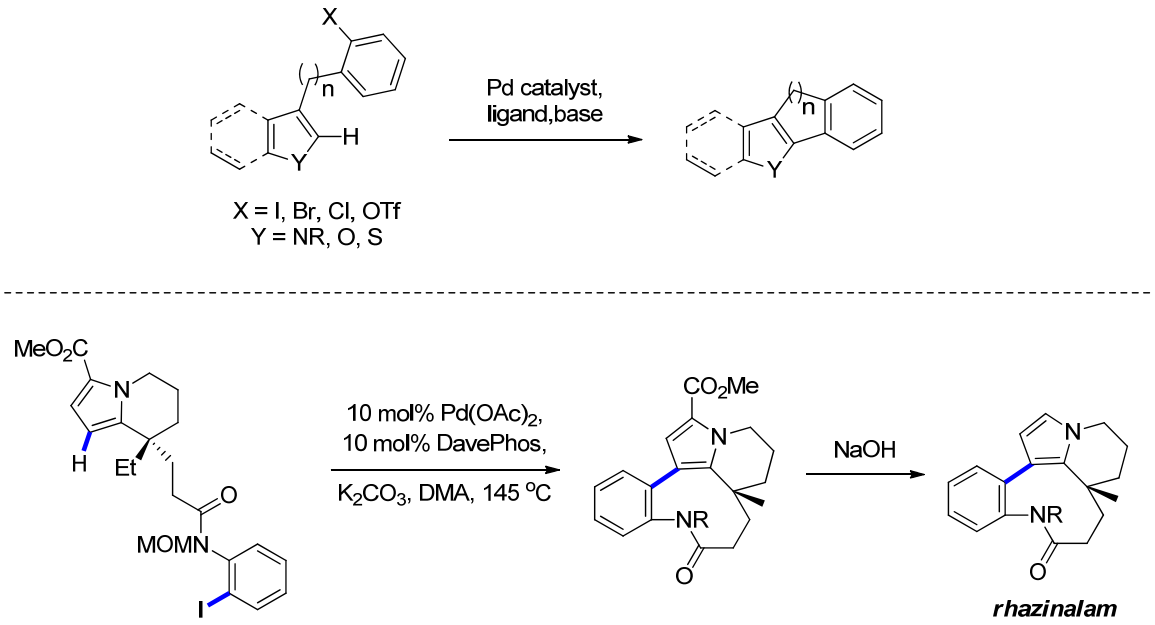


Scheme 24. Intramolecular and intermolecular, rhodium-catalyzed alkylation of azole heterocycles via hydroheteroarylation of alkenes

Although most methods for the functionalization of heteroarenes involve C-C bond formation, methods for C-N bond formation via heteroaromatic C-H functionalization have been developed. Cu-catalyzed amination of oxazoles and benzoxazoles with chloramines or hydroxylamine derivatives was developed by Miura and co-workers (Scheme).[90-91] This transformation likely occurs via deprotonation and transmetallation of the heteroarenes with the copper catalysts, followed by oxidative addition of the chloramines. Reductive elimination then forms the new C-N bond and

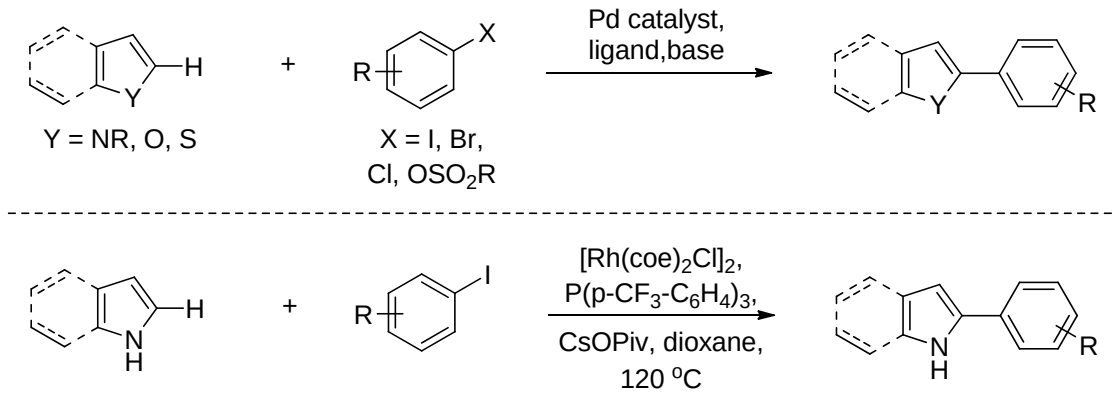
regenerates the low-valent copper catalyst. An oxidative approach to azole amination has also been developed.[92]

Several methods for C-H functionalization of heterocycles bearing one heteroatom have been developed. The vast majority of methods for direct C-H functionalization of pyrroles, indoles, furans, benzofurans, thiophenes and benzothiophenes for new C-C bonds at the 2-position or 3-position of these heterocycles (Scheme 25). Early examples focused on intramolecular direct arylation with tethered aryl halides or aryl pseudohalides catalyzed by palladium complexes in the presence of base. While formation of 5-membered and 6-membered rings by this cyclization strategy is most common, intramolecular direct arylation to form 7-membered and 8-membered rings has also been reported. A particularly active catalyst from the combination of $Pd(OAc)_2$ with DavePhos (2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl) as the ancillary ligand has been reported by Fagnou and co-workers.[93] This catalytic protocol has been utilized by Trauner[94] and Fagnou[95] in natural product total syntheses.



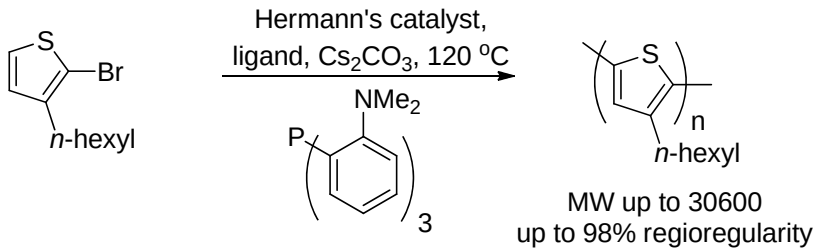
Scheme 25. Intramolecular direct arylation of heterocyclic C-H bonds with aryl halides and pseudohalides and application in total synthesis

Following demonstration of methods for intramolecular direct arylation, approaches to intermolecular direct arylation have developed. Arylation can be conducted with aryl halides and aryl pseudohalides with a variety of palladium catalysts. Arylation generally occurs at the 2-position, but in some cases the site-selectivity can be altered and arylation occurs at the 3-position.[96-97] In addition to methods utilizing palladium catalysts, Sames and co-workers have developed rhodium catalysts bearing electron-deficient aryl phosphine ligands for C-2 selective arylation of pyrroles and indoles with aryl iodides (Scheme 26).[98]



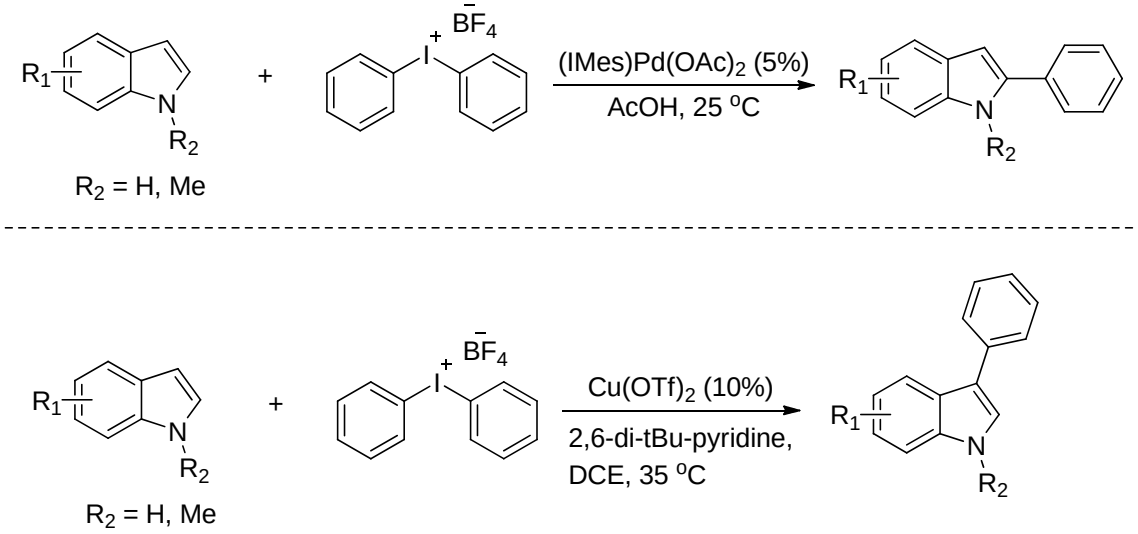
Scheme 26. Intermolecular, direct arylation of heteroarenes with aryl halides

Direct arylation of thiophenes is of particular interest because poly(3-alkyl)thiophenes are utilized as π-conjugated polymers for the construction and development of flexible electronic devices.[99] This class of polymers has been traditionally prepared by palladium-catalyzed cross-coupling of bifunctional thiophenes bearing an aryl bromide or iodide and an organometallic functionality, such as Mg, SnR_3, ZnX or $B(OR)_2$. While these approaches enable polymer synthesis, a potentially more direct route to these polymers would be to utilize direct arylation of thiophenes to perform the polymerization. Ozawa and co-workers have developed an effective method for the polymerization of 3-alkyl-2-bromothiophenes catalyzed by the combination of Hermann's catalyst and tris(*o*-*N*,*N*-dimethylaminophenyl)phosphine) as the ancillary ligand (Scheme 27).[100] This method enabled the synthesis of poly(3-hexylthiophene) with a high molecular weight and excellent regioregularity.



Scheme 27. Application of thiophene direct arylation for synthesis of poly(3-hexylthiophene)

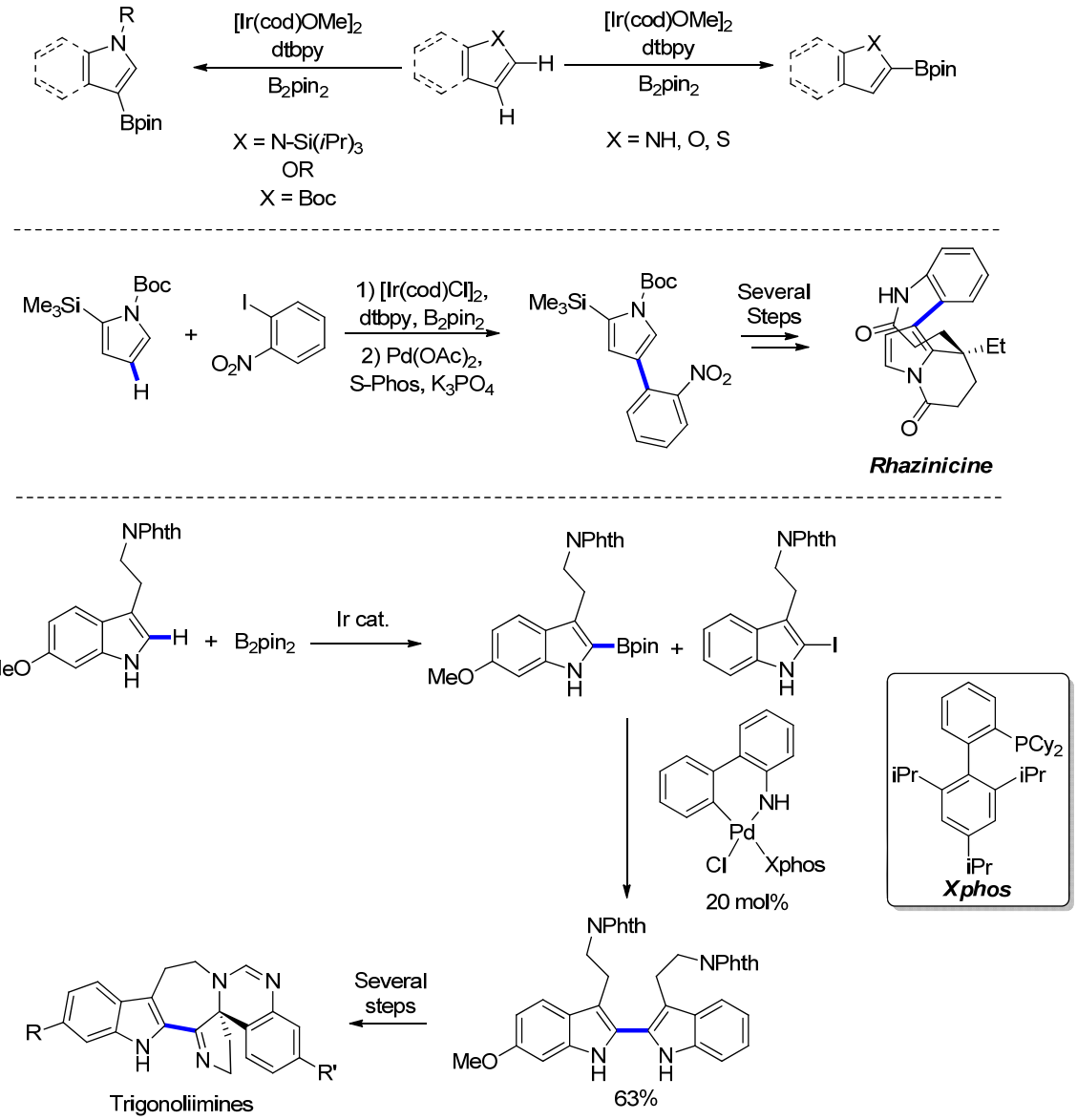
In addition to direct arylation with aryl halides, transition metal catalysts have been used for electrophilic C-H functionalization of heteroarenes with aryliodonium salts (Scheme 28). Electrophilic palladium catalysts, formed from oxidation with an aryliodonium salt, have been used to promote C-2 selective arylation of indoles.[101] In this methodology, indoles and pyrroles with a variety of substituents are arylated with diaryliodonium salts in the presence of $(IMes)Pd(OAc)_2$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) to yield 2-arylindole products in good yields. Although these examples occur with electron-deficient catalysts, arylation occurs at the most acidic C-H bond. Electrophilic copper complexes allow for another approach to indole arylation. With $Cu(OTf)_2$ as the precatalyst, arylation of indoles occurs at the 3-position with an aryliodonium salt as both the source of the aryl group and the oxidant.[102] In this reaction, a Cu(III) intermediate formed from oxidation of the copper precatalyst with the aryliodonium salt likely is the species that performs the C-H cleavage, which occurs at C-3, the most nucleophilic site. The use of an electrophilic copper catalyst provides a change in site-selectivity for indole arylation with aryl iodonium salts.



Scheme 28. Pd- and Cu-catalyzed arylation of indoles with aryliodonium salts

Iridium-catalyzed C-H borylation also occurs with heteroaromatic C-H bonds (Scheme 29). In contrast to the borylation of arene C-H bonds, the iridium-catalyzed borylation of the heteroaromatic C-H bonds of 5-membered ring heteroarenes and benzofused heteroarenes occurs at the C-H bond adjacent to the heteroatom (2-position).[103-105] the site-selectivity of iridium-catalyzed C-H borylation can be altered in pyrrole or indole heterocycles by incorporation of a bulky group, such as a tri-isopropylsilyl group or *tert*-butoxycarbonyl group, as the substituent on the nitrogen atom. In these cases, borylation occurs at the 3-position of pyrroles or indoles with high site-selectivity.[106] The borylation of 5-membered ring is facile, and the borylation on many of these substrates can be conducted at room temperature in high yield. In addition, the borylation of quinoline occurs predominantly at the 3-position of quinoline, and no borylation occurs on the benzene ring of quinoline. As with the iridium-catalyzed borylation of arenes, iridium-catalyzed borylation of heteroarenes has been utilized in natural product total synthesis. Iridium-catalyzed C-H borylation of a tryptamine derivative and subsequent Pd-catalyzed Suzuki-Miyaura cross-coupling with a heteroaryl

iodide was used by Movassaghi and coworker in the synthesis of several members of the Trigonoliimine class of natural products (Scheme 29).[107] Borylation of a pyrrole followed by Suzuki-Miyaura cross-coupling of the resulting heteroaryl boronate ester was a key step in the total synthesis of Rhazinicine by Gaunt and co-workers.[108]



Scheme 29. Site-selectivity of iridium-catalyzed borylation of heteroarenes and utilization in total synthesis

1.4 Summary and Objectives

While not comprehensive, this review summarizes many of the major developments in methods for the transition metal-catalyzed functionalization of aromatic and heteroaromatic C-H bonds. Clearly, transition metal catalysis has allowed for tremendous progress in the control of site-selectivity in arene functionalization, as well in the variety of functionality that can be appended to an aromatic framework. These methods have had a significant impact on the methods used to assemble complex molecules with a variety of functions. Due to the increasing demand for more direct synthetic methods which product less waste and operate under more mild conditions, the development of these methods will surely continue at a rapid pace in the future. To contribute to this further development of effective C-H functionalization reactions which address unmet challenges in synthetic methodology, the work described in subsequent chapters in this thesis will describe the following contributions:

1) The development of a general method for the *meta*-selective alkylation of arenes via iridium-catalyzed C-H borylation and subsequent Pd- or Ni- catalyzed cross-coupling of the resulting pinacol boronate ester with various alkyl electrophiles. (Chapter 3)
2) The use of the pinacol boronate esters formed via iridium-catalyzed of heteroarenes and fluoroarenes as surrogates for unstable boronic acids in Suzuki-Miyaura cross-coupling with aryl halides under mild reaction conditions. (Chapter 4)
3) The development of a synthetic method for the iridium-catalyzed, silyl-directed borylation of nitrogen-containing heterocycles which allows for the access to

substituted heterocycles that would be difficult to access by other methods. (Chapter 5)

1.5 References

(1) Trost, B. *Science* **1991**, *254*, 1471.

(2) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2007**, *41*, 40.

(3) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(4) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

(5) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

(6) Bergman, R. G. *Nature* **2007**, *446*, 391.

(7) Hartwig, J. F. *Nature* **2008**, *455*, 314.

(8) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(9) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.

(10) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

(11) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 458.

(12) Grushin, V. V.; Marshall, W. J.; Thorn, D. L. *Adv. Synth. Catal.* **2001**, *343*, 161.

(13) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2000**, *123*, 337.

(14) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(15) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

(16) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(17) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2011**.

(18) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652.

(19) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081.

(20) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203.

(21) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *134*, 134.

(22) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916.

(23) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058.

(24) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855.

(25) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534.

(26) Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092.

(27) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201.

(28) Kakiuchi, F.; Sato, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, *28*, 19.

(29) Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647.

(30) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522.

(31) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.

(32) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783.

(33) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772.

(34) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624.

(35) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(36) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2011**.

(37) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

(38) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

(39) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668.

(40) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463.

(41) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298.

(42) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270.

(43) Dudnik, A. S.; Chernyak, N.; Huang, C.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 8729.

(44) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(45) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

(46) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350.

(47) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

(48) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

(49) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305.

(50) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *124*, 390.

(51) Liskey, C. W.; Wei, C. S.; Pahls, D. R.; Hartwig, J. F. *Chem. Commun.* **2009**, 5603.

(52) Iwadate, N.; Suginome, M. *J. Organomet. Chem.* **2009**, *694*, 1713.

(53) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758.

(54) Hartwig, J. F. *Acc. Chem. Res.* **2011**.

(55) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792.

(56) Shi, F.; Smith, M. R.; Maleczka, R. E. *Org. Lett.* **2006**, *8*, 1411.

(57) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761.

(58) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.

(59) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(60) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.

(61) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 536.

(62) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem. Int. Ed.* **2012**, *51*, 540.

(63) Tajuddin, H.; Shukla, L.; Maxwell, A. C.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2010**, *12*, 5700.

(64) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

(65) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088.

(66) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946.

(67) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072.

(68) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964.

(69) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090.

(70) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(71) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332.

(72) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.

(73) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448.

(74) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887.

(75) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666.

(76) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(77) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M. g.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

(78) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254.

(79) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

(80) Liégault, B. t.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(81) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, *2006*, 693.

(82) Pivsa-Art, S.; Fukui, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2039.

(83) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

(84) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 12307.

(85) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493.

(86) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1589.

(87) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685.

(88) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964.

(89) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202.

(90) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900.

(91) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860.

(92) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.

(93) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186.

(94) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207.

(95) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849.

(96) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

(97) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 8946.

(98) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

(99) Osaka, I.; McCullough, R. D. *Acc. Chem. Res.* **2008**, *41*, 1202.

(100) Wang, Q.; Takita, R.; Kikuzaki, Y.; Ozawa, F. *J. Am. Chem. Soc.* **2010**, *132*, 11420.

(101) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

(102) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(103) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103.

(104) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

(105) Chotana, G. A.; Kallepalli, V. A.; Maleczka Jr, R. E.; Smith III, M. R. *Tetrahedron* **2008**, *64*, 6103.

(106) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199.

(107) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768.

(108) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3004.

Chapter 2. Overview of Approaches to Reaction and Catalyst Discovery Based Upon High-Throughput Screening

2.1 Introduction

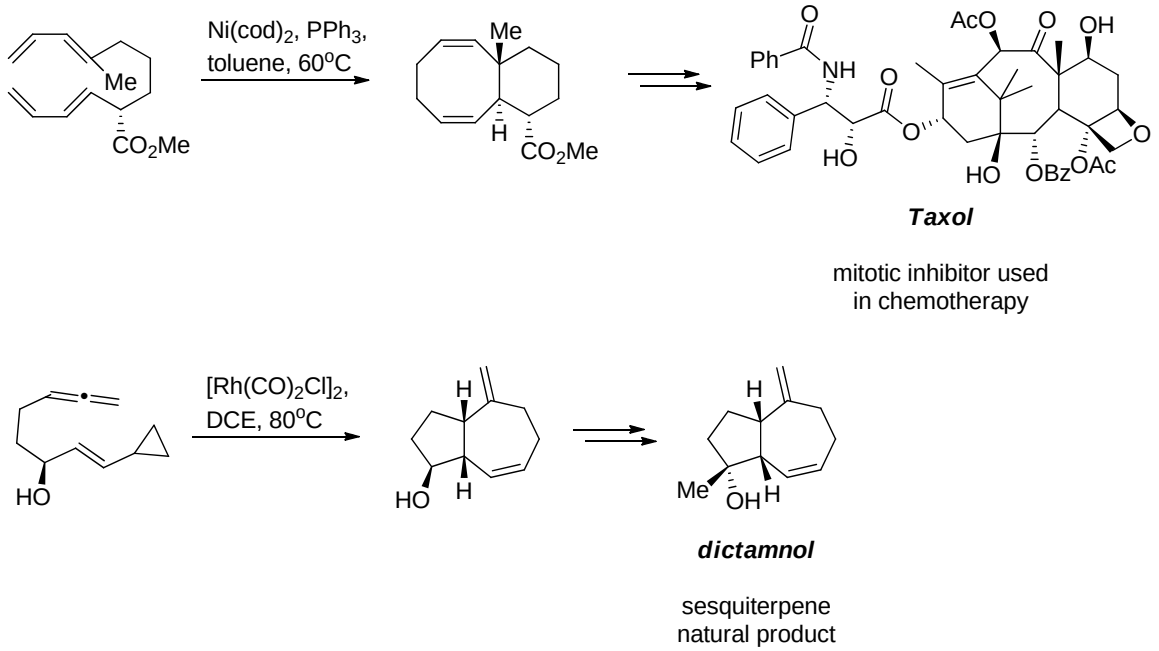
The discovery of new chemical reactions provides essential tools that can enable organic synthesis and significantly accelerate advances in many areas of science.[1] While reaction discovery in many fields continues, catalytic reactions involving transition metals have grown into some of the most commonly used methods for the construction of many classes of molecules. Transition metal complexes catalyze many important reactions used in medicine,[2] materials science[3-4] and energy production,[5-6] making development of new metal-catalyzed processes highly attractive in both academic and industrial settings. It is estimated that transition metal catalysis contributes to approximately one-quarter of the economy of the United States, which highlights the importance of these technologies in a variety of applications with tremendous value.[7]

2.2 General drivers for the discovery of new chemical reactions

2.2.1 Reaction discovery driven by synthesis of a target molecule or target structure

Several approaches have proven successful in discovering and developing transition metal catalysts for applications in synthetic chemistry. One approach has focused on developing an organometallic catalyst for a specific bond construction or for a specific structural feature found in a target molecule or class of target molecules. An example of this approach can be seen in the work of Wender and co-workers in developing novel, transition metal-catalyzed cycloaddition reactions of alkenes, allenes, alkynes, and other unsaturated moieties to form unusual carbocycles, including 7-membered and 8-membered rings (Scheme 30).[8,9] For example, Wender and Snapper

utilized a nickel-catalyzed [4+4] cycloaddition of two 1,3-diene units to construct the 8-membered ring at the core of paclitaxel, the active ingredient in Taxol, a common chemotherapeutic agent.[10] Wender and co-workers have also utilized a rhodium-catalyzed [5+2] cycloaddition of an allene and a vinylcyclopropane to construct the bicyclic structure of dictamnol, a sesquiterpene natural product.[11]

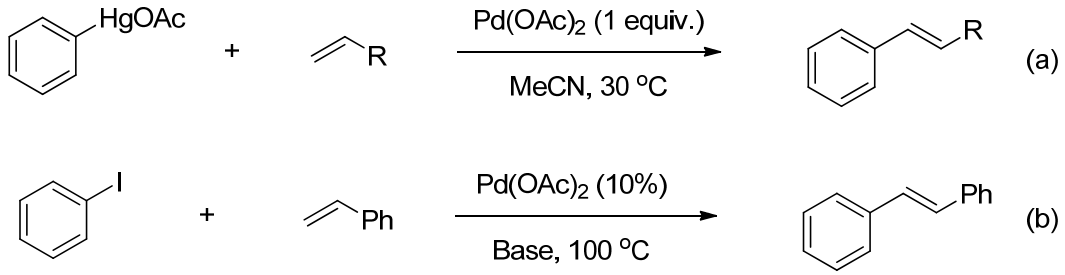


Scheme 30. Transition-metal catalyzed cycloaddition reactions for the synthesis of core structures of natural products

2.2.2 Reaction discovery driven by fundamental reactivity of a catalyst

In addition to catalyst discovery motivated by the synthesis of a target structure, the discovery and development of transition metal-catalyzed reactions can be inspired by the fundamental reactivity of organometallic complexes. While there are many examples of mechanistic understanding leading to useful catalytic chemistry, one of the most prominent examples is the development of the Mizoroki-Heck reaction from fundamental studies of the reactivity of arylpalladium complexes with olefins. In landmark studies in

this area, Heck demonstrated that transmetallation of an aryl mercury compound with $Pd(OAc)_2$ forms an arylpalladium complex. This arylpalladium complex then undergoes reaction with an olefin to form a vinylarene, presumably through olefin coordination, olefin insertion, and β-hydride elimination (Scheme 31a).[12] While this study provides crucial understanding of the fundamental reactivity of arylpalladium complexes with olefins, it does not represent a useful synthetic process, primarily because it uses a toxic mercury reagent and a stoichiometric quantity of the palladium salt. However, with this fundamental knowledge, Mizoroki and Heck developed a catalytic reaction that allows for coupling of aryl halides with olefins with catalytic quantities of palladium (Scheme 31b).[13-14] From this initial discovery, highly active palladium catalysts have been discovered,[15-17] and the Mizoroki-Heck reaction has evolved into one of the most commonly used cross-coupling reactions in the synthesis of complex small molecules.[18]

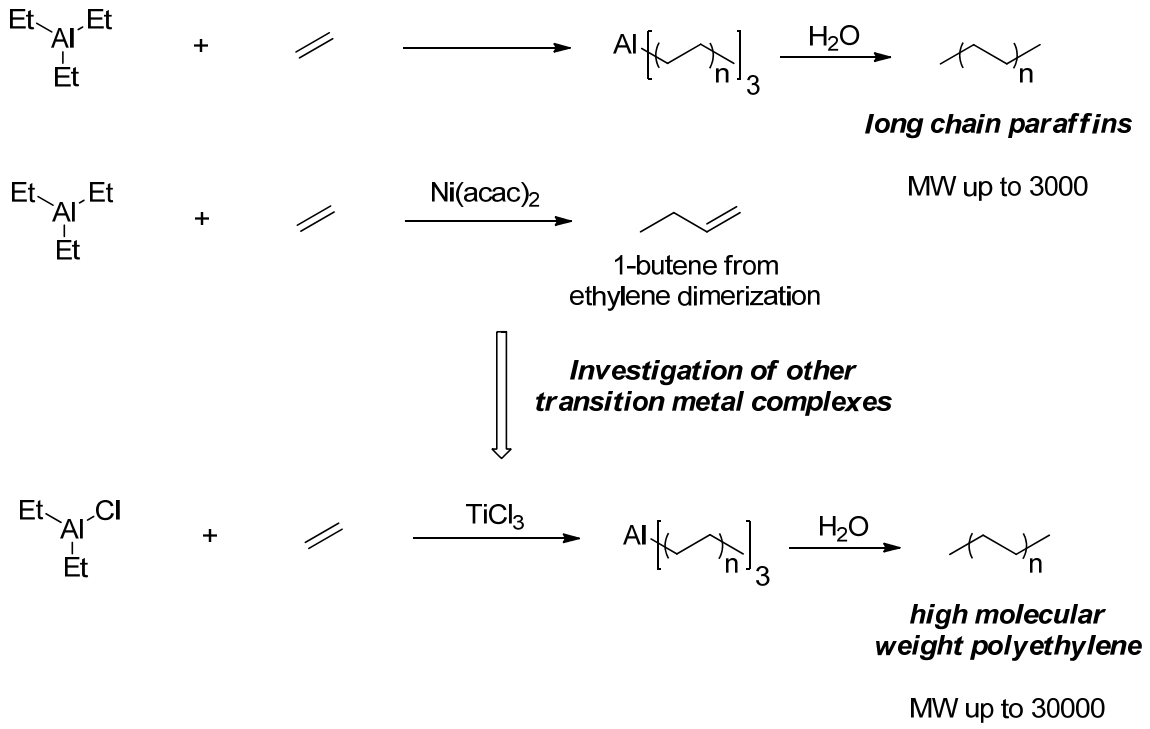


Scheme 31. Stoichiometric reactivity of arylpalladium complexes with olefins, leading to development of the Mizoroki-Heck reaction

2.2.3 Reaction discovery initiated by a serendipitous observation

Along with reaction discovery motivated by the synthesis of a key organic structure or inspired by the fundamental, stoichiometric reactivity of an organometallic complex, several transition metal-catalyzed reactions have been discovered serendipitously while seeking other outcomes. One of the most commercially important

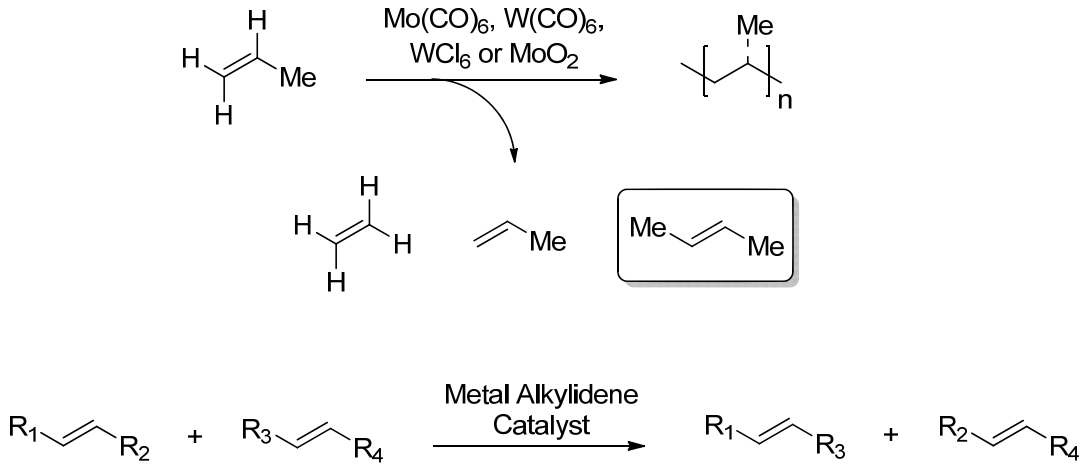
examples of this type of catalyst discovery is the initial identification of organometallic catalysts for ethylene polymerization. Ziegler and co-workers had demonstrated that the reaction of alkyl aluminum compounds with ethylene afforded trialkylaluminum compounds with increased molecular weight (Scheme 32). However, inadvertent contamination of the reaction vessel with Ni salts hindered ethylene oligomerization and resulted in ethylene dimerization to form 1-butene. This serendipitous discovery led Ziegler and co-workers to the crucial insight that a transition metal complex could affect the reaction of aluminum alkyl compounds with olefins. Following this insight, Ziegler and co-workers performed a systematic investigation of other metal salts to affect the oligomerization of ethylene. These investigations resulted in the identification of $TiCl_3$ and Et_2AlCl as a highly active catalyst for olefin polymerization. Ti/Al catalysts are now known as Ziegler-Natta polymerization catalysts and are used on a large, industrial scale to produce more than 40 million tons of polyolefins each year.[19]



Scheme 32. Serendipitous discovery of the effect of transition metal complexes on the polymerization of ethylene

Olefin metatheis is another example of serendipitous discovery of a new, metal-catalyzed reaction. While attempting to discover transition metal catalysts for the polymerization of propylene, Eleuterio, working at DuPont, analyzed the off gas from this process and determined that in addition to propylene, ethylene and butene were formed (Scheme 33).[20] Because ethylene and butene cannot be formed from oligomerization of propylene, it was determined that ethylene and butene must have formed from redistribution of the olefin fragments. This discovery led to the identification of transition metal-catalyzed olefin metathesis as a viable synthetic process. Since that initial, serendipitous discovery, the mechanism of olefin metathesis has been delineated, highly active catalysts have been developed, and olefin metathesis has found

widespread use of in the synthesis of natural products and even in commercial applications to synthesize functional polymeric materials.[21-27]



Scheme 33. Serendipitous discovery of transition metal catalysts for olefin metathesis

2.3 Reaction discovery via high-throughput screening

While these general approaches to the discovery of fundamentally new chemical transformations have resulted in important contributions to the development of synthetic methodology, another potential approach to the discovery of new catalysts and new synthetic transformations is through the high-throughput evaluation of catalyst and substrate combinations. High-throughput screening has been used in the discovery of lead compounds in drug discovery,[28] medicinal chemistry,[29] and to discover new classes of materials for materials science applications.[30-33] Inspired by these successes, many chemists have begun to utilize high-throughput screening for catalyst identification and optimization in a variety of different catalysis applications.[34-35] These approaches for catalyst discovery can generally be placed into one of three different categories based upon the areas or dimensions of potential chemical space that are surveyed:

1) Examination of many catalysts for the discovery and optimization of a catalyst for a single chemical transformation

2) Examination of a single catalyst with many different substrates for the potential discovery of a new bond construction or a new catalyst for an existing bond construction
3) Examination of many catalysts and many organic substrates for the potential discovery of new catalysts and new strategies for bond construction

This chapter will review approaches to the discovery, development or optimization of catalysts with high-throughput screening techniques.

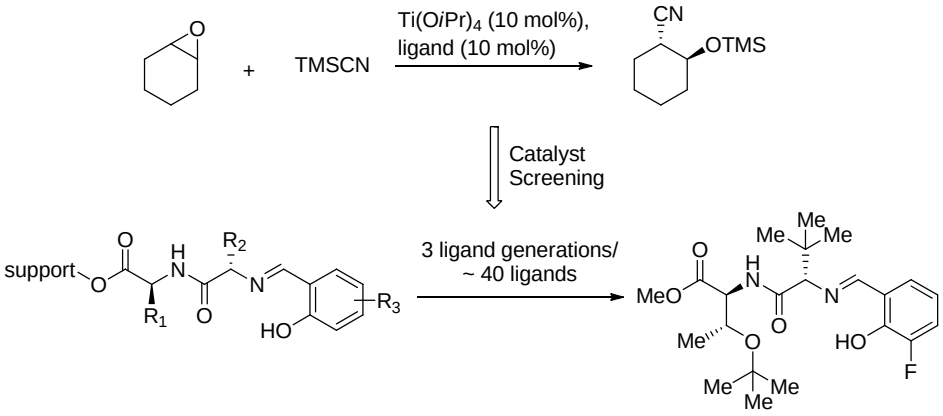
2.3.1 Examination of many catalysts for the discovery and optimization of a catalyst for a single chemical transformation

One approach to high-throughput screening in catalysis focuses on a single reaction, between two substrates, and surveys a variety of potential catalysts. Within transition metal catalysts, the steric and electronic properties of the metal complex generally control the reactivity of the catalyst. Because it is very difficult to generate a general catalyst structure for a new catalytic reaction or to design an optimal catalyst for a specific transformation *de novo*, combinatorial examination of catalysts has emerged as an attractive strategy for catalyst development for both academic and industrial applications.

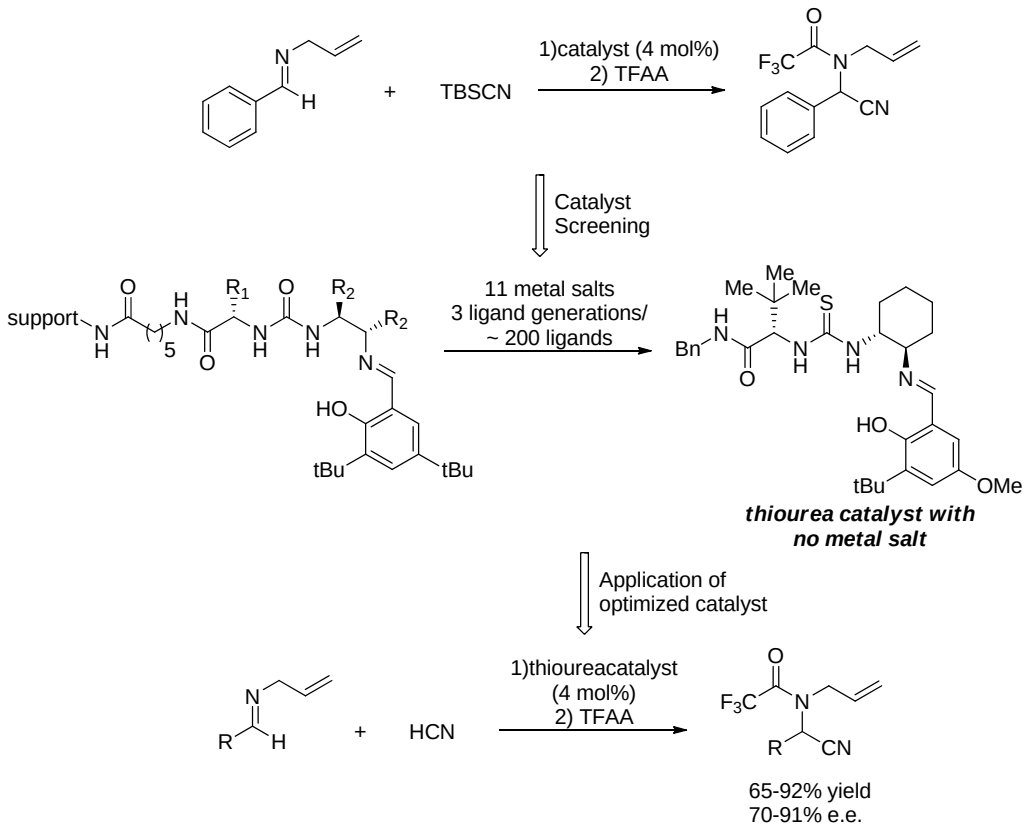
Libraries of catalysts have been used for discovery and optimization of a single synthetic transformation. Hoveyda and co-workers and Jacobsen and co-workers have utilized solid-phase synthesis to construct libraries of chiral small molecules for various applications in asymmetric catalysis (Scheme 34). Hoveyda and co-workers synthesized a small library of peptide-based catalysts and utilized these ligands in combination with $Ti(O\textit{i}Pr)_4$ to develop the first method for the catalytic, enantioselective addition of TMSCN to *meso*-epoxides.[36] In a similar approach, Jacobsen and Sigman examined a

small library of (thio)urea catalysts for the asymmetric addition of cyanide to imines.[37] In this approach, a series of transition metal salts and urea-based ligands were examined, and the best results were obtained in the absence of a metal salt. Further catalyst optimization revealed a thiourea catalyst that enabled the addition of HCN to imines with good yield and generally high enantioselectivity. Both of these methods begin with iterative construction of libraries based upon the identification of "lead" catalysts, followed by rational variation and optimization of the key molecular elements of the catalyst structure. Most notably, both of these approaches led to the discovery of classes of catalysts that have been developed further into a variety of useful methodologies in asymmetric catalysis.[38-43] The use of ligand libraries has also been applied to the discovery of catalysts for other applications, including C-H insertion reactions[44] and Ullmann coupling.[45]

Screening of peptide-based ligands for enantioselective opening of epoxides:



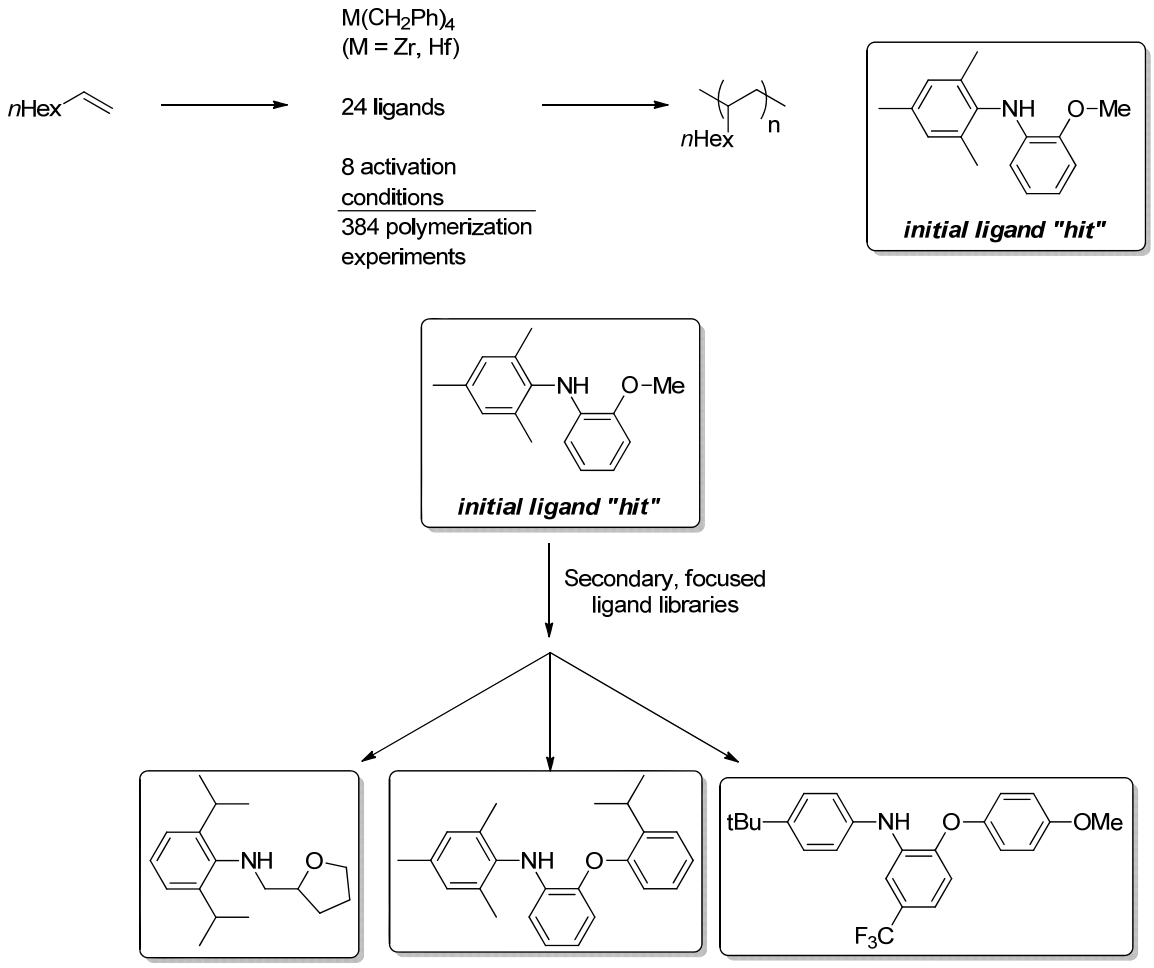
Screening of (thio)urea-based ligands for the enantioselective Strecker reaction:



Scheme 34. Use of libraries of chiral catalysts for the discovery of useful methods for the catalytic, asymmetric addition of cyanide to *meso*-epoxides and the catalytic, asymmetric Strecker reaction

High-throughput screening of organometallic complexes has also been used to discover new catalysts for olefin polymerization.[46-48] Several different approaches have been adopted to discover new single-site olefin polymerization catalysts as well as new organometallic complexes for olefin metathesis polymerization. In addition to solid phase synthesis techniques, Murphy and co-workers utilized a fully integrated method to examine early metal olefin polymerization catalysts for the co-polymerization of ethylene and 1-octene (Scheme 35). These catalysts product linear low-density polyethylene (LLDPE), an important commercial polymer. In this approach, an initial screen of bidentate and tridentate ligands with early metal alkyl complexes in combination with several different potential activators was conducted for the polymerization of 1-octene. Although a copolymer of ethylene and 1-octene is the final target, because ethylene generally undergoes olefin insertion more rapidly than does 1-octene, it was hypothesized that a catalyst which provides rapid and high-yielding polymerization of 1-octene would effectively co-polymerize ethylene and 1-octene. In the initial catalyst screen, 2 catalyst precursors, 24 ligands and 8 distinct activation conditions were examined for polymerization of 1-octene. Rapid GPC was the analysis tool, and a ligand derived from an aminoalcohol was selected to provide the general ligand structure for further optimization. A secondary library of ligands was then synthesized and screened with a Hf catalyst precursor, and several ligands were discovered that enable ethylene and 1-octene co-polymerization with high molecular weight and high chemical yield.[47] Because

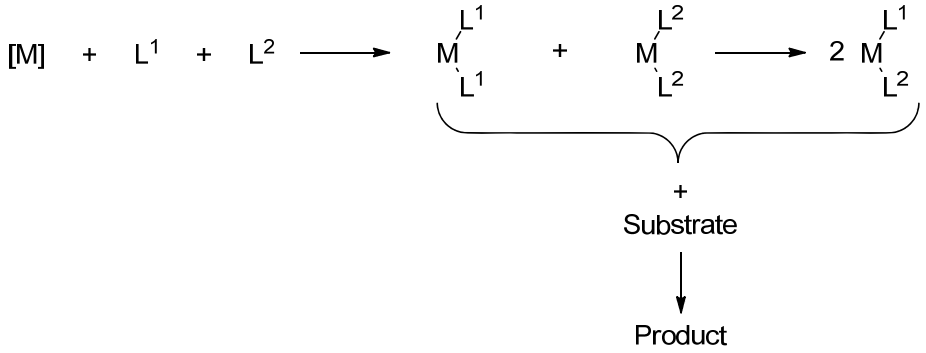
automated robotic equipment was used for assembly of the individual reaction and rapid GPC was used as the analysis tool, all of these catalysts can be screened extremely rapidly, accelerating the timeline for catalyst discovery. Catalysts of this type are now used at Dow Chemical to produce polyolefins and block co-polymers on an industrial scale for a variety of commercial applications.



Scheme 35. High-throughput screening of early metal catalysts for the co-polymerization of ethylene and 1-octene

Simultaneous screening of multiple ancillary ligands with a single transition metal complex in solution is another strategy for high-throughput screening of transition metal

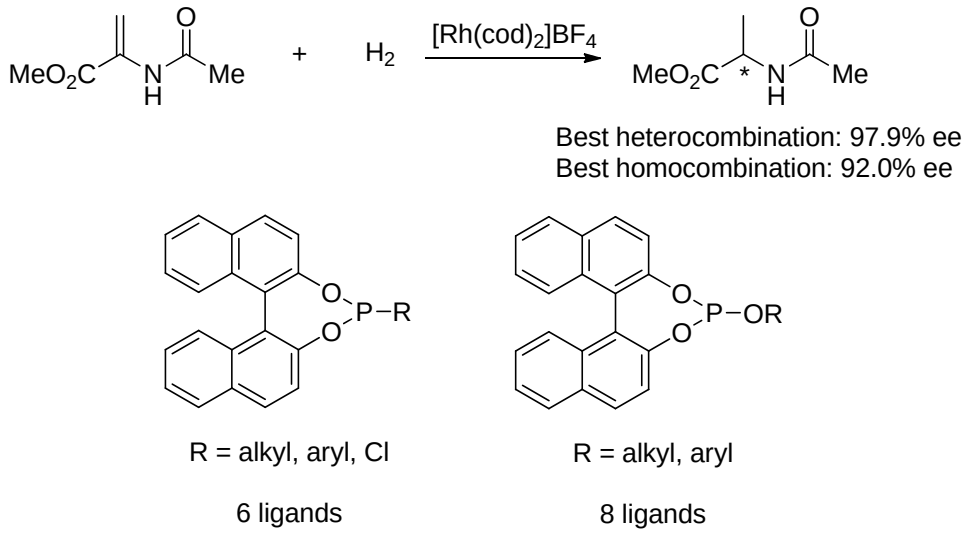
catalysts. In these approaches, mixtures of ligands are combined with a single transition metal catalyst precursor, and these mixtures are evaluated for a single catalytic transformation (Scheme 36). While scientists generally seek a single, well-defined homogeneous catalysts, this approach demonstrates that mixtures of catalysts can be used effectively for the purposes of catalyst discovery and development, generally for applications in asymmetric homogenous catalysis.[49]



Scheme 36. Use of two distinct monodentate ligands for formation of homoleptic and heteroleptic complexes for catalyst screening

One of the first demonstrations of this strategy was by Reetz and co-workers in the investigation of new catalysts for asymmetric hydrogenation of enamides. In this investigation, a rhodium precatalyst was mixed with two different monodentate phosphite or phosphinite ligands, and the efficacy of the catalysts formed *in situ* were examined for the asymmetric hydrogenation of an enamide substrate (Scheme 37).[50] A relatively small library of just 14 ligands was examined, which allows for up to 91 potential heteroleptic catalysts. With this technique, it was discovered that combinations of 2 different ligands could form active catalysts for asymmetric hydrogenation, and that these catalysts could provide higher enantioselectivity than even the best catalysts formed from 2 of the same ligand. This approach to the discovery of chiral catalysts has been extended to conjugate

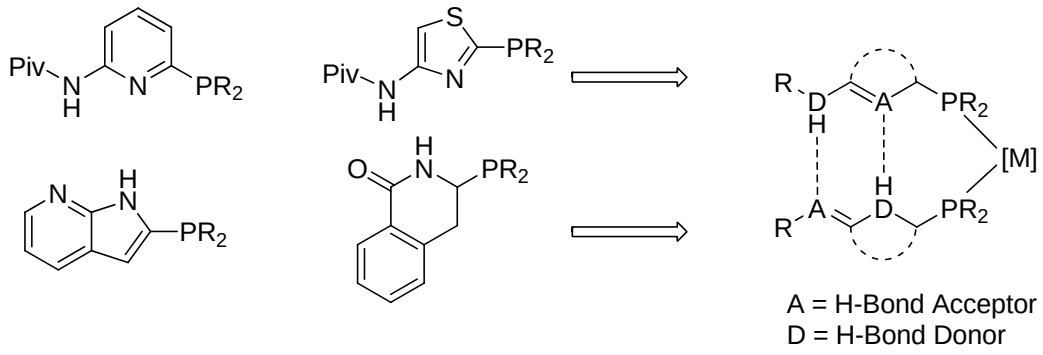
addition of organoboron compounds to enones.[51] Other forms of reaction and catalyst selectivity have been examined with achiral, monodentate ligands, including site-selectivity of hydroformylation[52] and diastereoselectivity of imine reduction.[53]



Scheme 37. Screening of mixtures of monodentate ligands to discover catalysts for rhodium-catalyzed asymmetric hydrogenation

Supramolecular self-assembly can also be used to rapidly examine mixtures of catalysts for a given catalytic reaction.[54] Breit and Seiche pioneered this approach by applying hydrogen bonding non-covalent interactions based upon Watson-Crick base pairing of two molecules, each containing a recognition element and a functional group, to serve as an ancillary ligand within a transition metal complex (Scheme 38).[55] This approach allows for positioning of two monodentate ligands around a metal center to form a self-assembled bidentate ligand, which alleviates the often-tedious process of synthesizing a library of bidentate ligands. The combination of a variety of monodentate ligands with various steric and electronic effects would essentially allow for rapid examination of a wide variety of pseudobidentate ligands. With this approach to catalyst discovery, rhodium catalysts were identified for site-selective hydroformylation to form

linear aldehydes[55] and alkene hydrocyanation.[56] While these approaches led to the discovery of new catalysts, they require large numbers of individual reactions involving two ligands, a metal catalyst precursor and the reactive substrates. A significant advance in the application of ligand self-assembly for transition metal catalysis was developed by Wieland and Breit in the screening of rhodium catalysts for asymmetric hydrogenation.[57] In this study, they demonstrated that mixtures of a single catalyst precursor and a library of ligands with molecular recognition functionalities to allow for the self-assembly of combinations of ligands in the reaction mixture could be utilized to accelerate catalyst discovery. An iterative deconvolution strategy was devised to identify the active catalyst that provided high yield and enantioselectivity for rhodium-catalyzed asymmetric hydrogenation of enamides. For deconvolution, the catalyst library was divided into four groups. The rhodium precatalyst and the substrate was added to each group of ligand mixtures, the hydrogenation was conducted, and the enantioselectivity and yield was determined. The ligands in the group which catalyzed the hydrogenation with the highest yield and enantioselectivity were then selected and the other ligands were eliminated. Two further iterations of this process led to the most active catalyst for this hydrogenation reaction.

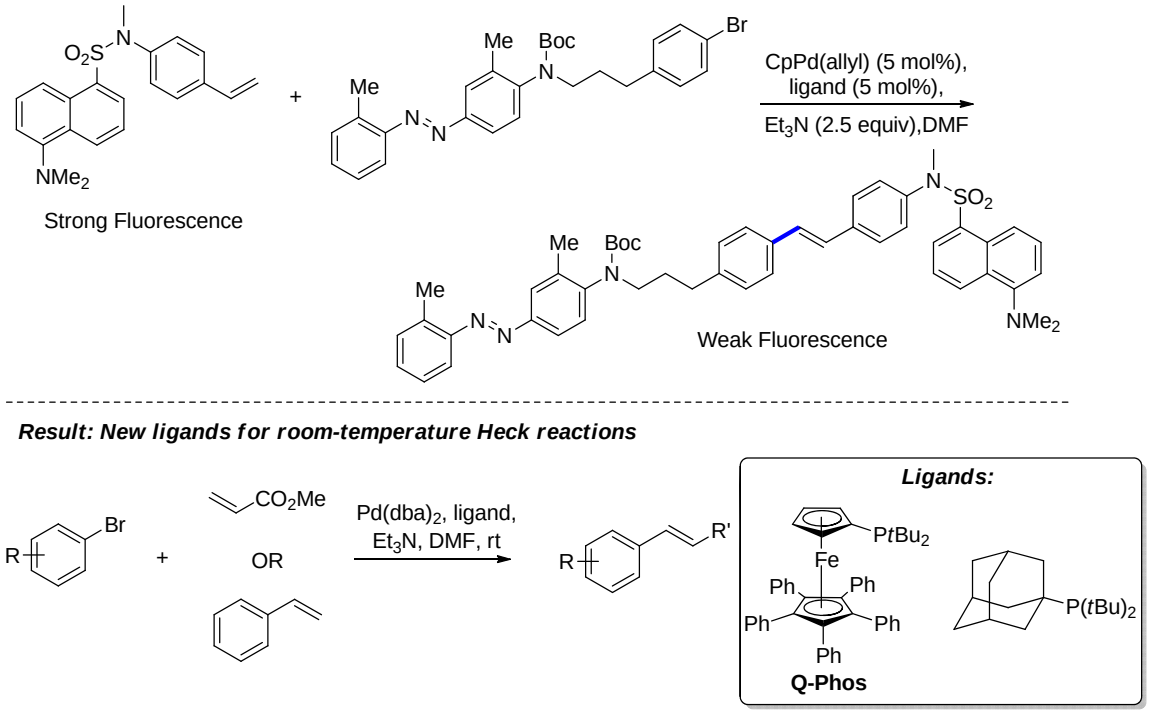


Scheme 38. General approach for the use of supramolecular self-assembly for the high-throughput screening of ligand libraries

In similar work, Reek, van Leeuwen and co-workers have used a metal binding template as the organizational element in supramolecular self-assembly of ligand systems for catalyst screening.[58] While these approaches to examine mixtures of ligands is an important contribution in the development of strategies for the high-throughput screening of catalysts, this approach has been applied primarily to asymmetric olefin hydrogenation, which is a relatively well-developed area in homogenous catalysis.[59-61] Future investigations to discover new catalysts that address synthetic challenges for which there are few current solutions will further highlight the value of this approach to catalyst screening.

Previously described approaches involving ligand libraries and self-assembled bidentate ligands for catalyst screening generally employ conventional product analysis techniques, such as gas chromatography (GC) and high-performance liquid chromatography (HPLC) for the analysis of small molecules and gel permeation chromatography (GPC) for polymer analysis. Fluorescence-based assays for the determination of catalyst activity are another approach to the high-throughput screening of transition metal complexes. This strategy has been used for the discovery of new

cross-coupling catalysts, including for Heck coupling,[15] arylation of enolates,[62] and Buchwald-Hartwig amination.[63] The use of a fluorescence assay for the discovery of a new catalyst for Heck coupling is an illustrative example. In this investigation of palladium catalysts for Heck coupling of aryl halides with vinylarenes, two substrates were specifically designed to utilized fluorescence resonance energy transfer (FRET) as an assay for catalyst activity (Scheme 39). The vinylarene substrate provides a strong fluorescence signal, but when it becomes covalently bonded to the aryl bromide substrate through the Heck coupling, the fluorescence is quenched, and the fluorescence signal becomes weak. The use of fluorescence as the reaction assay provides a rapid method for determination of the reaction yield because FRET can be measured with a standard plate reader and is quantitative. 96 different ligands were screened, and as a result, two highly active catalysts were identified.[15] These catalysts were formed from the combination of a Pd-precatalyst and either 1-adamantyl-di-tert-butyl phosphine or Q-Phos as the ancillary phosphine ligand. Both of these catalysts enabled room-temperature Heck reactions of aryl bromides. Because Heck reactions commonly require temperatures in excess of 100 °C, making a catalyst which enables Heck coupling at ambient temperature a significant advance in this area of cross-coupling.[64] Along with the discovery of Pd-catalysts for cross-coupling applications, Miller and co-workers have applied fluorescence-based assays for the discovery of small peptide catalysts[65] for the kinetic resolution of secondary alcohols[66] and for the site-selective derivatization of natural products.[67]



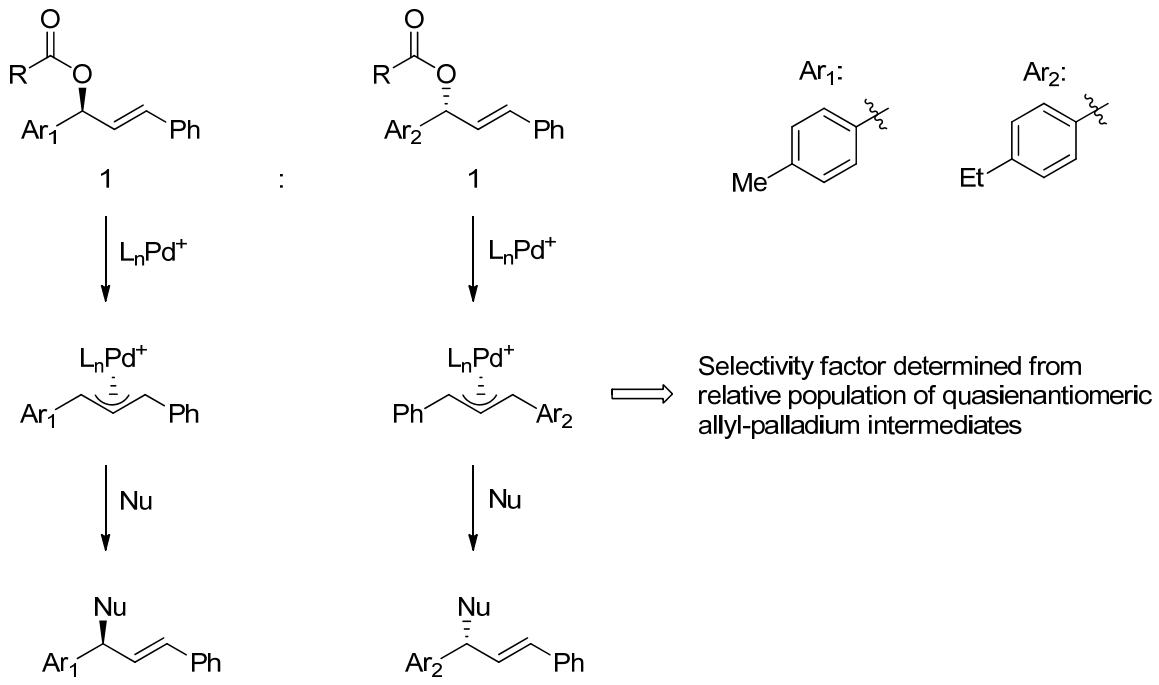
Scheme 39. Fluorescence assay for the discovery of palladium catalysts for room-temperature Heck reactions

Several innovative methods have been developed for the application of mass spectrometry as an analysis tool for high-throughput catalyst screening. Mass spectrometry is a particularly appealing and useful method for analysis of transition metal catalysts because it is very sensitive, does not require product purification, readily available in many laboratories, and is amenable to high-throughput analysis. Chen and co-workers developed a system that uses electrospray ionization (ESI) mass spectrometry to examine the activity of mixtures of catalysts in a single vessel for a single catalytic reaction.[48,68] This method relies upon the fact that ESI mass spectrometry detects charged species. Charged substrates, generally including a phosphonium or ammonium group, must be used to generate charged intermediates, which can then be detected by ESI mass spectrometry. This approach has been applied to the screening of catalysts for Ir-

catalyzed olefin hydrogenation,[69] Ru-catalyzed olefin metathesis,[70] C-H activation by Ir complexes,[71] and olefin polymerization.[72-73] A distinguishing feature of this method of catalyst screening is that it allows for analysis of the catalytic intermediates, not the analysis of the final products. Therefore, this approach measures the true activity of a catalyst, and this analysis is not influenced by other factors, such as product decomposition, changes in the active catalyst species, or catalysis which occurs by minor impurities often formed in the synthesis of organometallic complexes.

Based upon the work of Chen and co-workers, Pfaltz and co-workers have applied ESI mass spectrometry to rapidly examine catalysts for their performance in a variety of applications in asymmetric catalysis.[74] This technique relies upon the use of "quasienantiomeric" substrates and the examination and quantification of charged catalytic intermediates that are formed upon reaction of these substrates with an organometallic catalyst. This strategy was initially applied to palladium-catalyzed kinetic resolution of allylic esters (Scheme 40).[75] This particular reaction was selected because the mechanism is well understood, and most importantly, proceeds via the formation of cationic intermediates. The first step in this reaction is oxidative addition of the allylic ester to a Pd(0) complex to form an allyl-palladium complex. This intermediate then undergoes nucleophilic attack by an external nucleophile to form the allylic substitution product. Because nucleophilic attack is the turnover-limiting step of the catalytic cycle, the allyl-palladium intermediate is the catalyst resting state, indicating that it should be present in solution in high enough concentration to be observed with ESI-MS. Pfaltz and co-workers hypothesized that if two quasienantiomeric substrates were subjected to the activity of a chiral catalyst, the relative population of the two quasidiastereomeric allyl-

palladium intermediates should indicate the selectivity of the catalyst. When this experiment was conducted with a 1:1 mixture of quasienantiomeric allylic esters, one bearing a 4-methylphenyl group and one bearing a 4-ethylphenyl group, quasidiastereomeric mixtures of allylpalladium complexes were observed. In addition to examining ligands individually, mixtures of up to 5 ligands were examined simultaneously in the same reaction mixture to determine the selectivity of the catalysts formed from each of these ligands. After this rapid screening protocol was applied to a small library of P,N- ligand and chiral bisphosphine ligands, a new P,N-ligand in combination with $[Pd(C_3H_5)(MeCN)_2]OTf$, provided a 9:91 ratio of the two quasienantiomers, as observed by ESI-MS. After further optimization, a selectivity factor of 100 could be obtained for kinetic resolution of allylic esters, which represented the highest value obtained at the time of the work. This result exemplifies the utility of this approach to rapid screening of chiral catalysts. This general approach to chiral catalyst screening has been applied to other reactions, including desymmetrization of *meso* substrates via palladium-catalyzed allylic substitution[74] and enantioselective Diels-Alder reactions.[76] While this approach has been demonstrated to be useful for several applications, the primary limitation of this strategy for catalyst screening is that the reaction being examined must involve cationic intermediates, which inherently limits the scope and generality of this method. In addition to mass spectrometry, colorimetric assays,[77-78] isotopic labeling,[79-80] and infrared thermography[81] are useful tools for high-throughput analysis of catalyst libraries for various transformations.

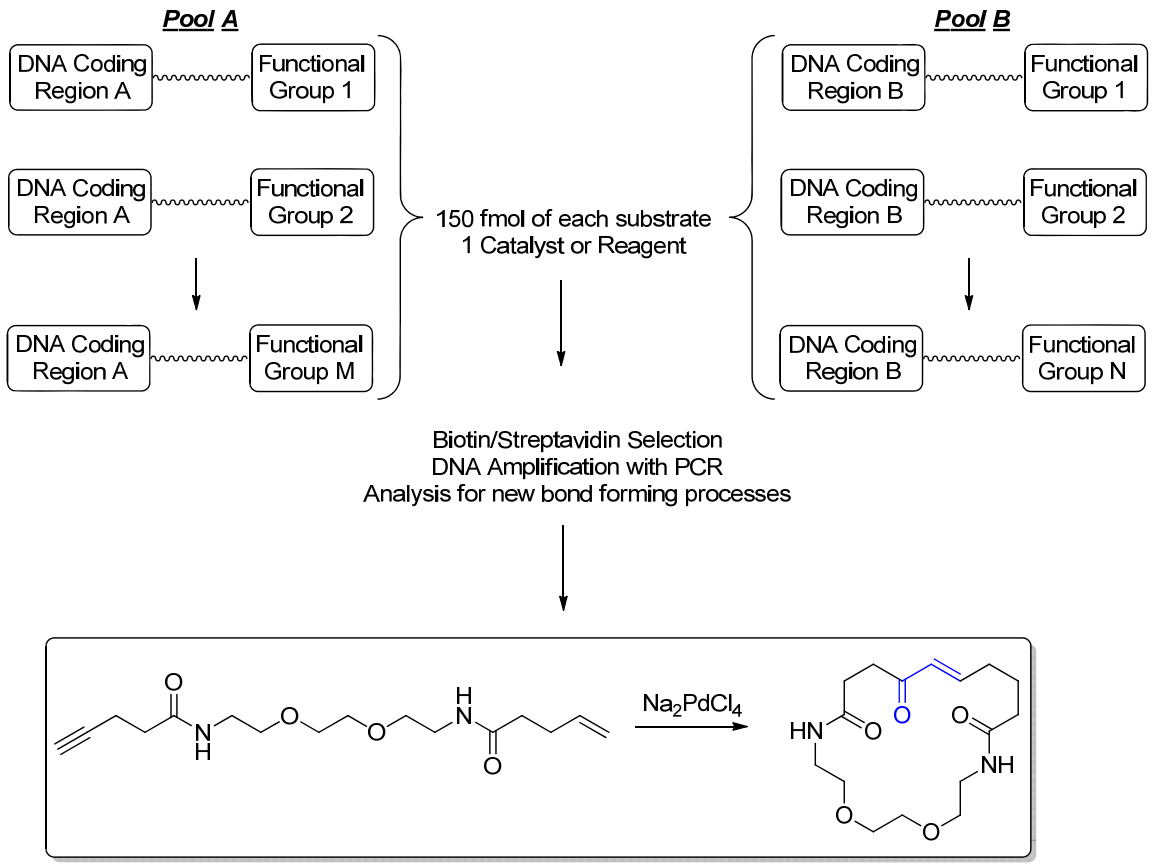


Scheme 40. Determination of selectivity factor of chiral palladium catalysts for kinetic resolution of allylic esters by screening of quasienantiomers by ESI-MS

2.3.2. Examination of a single catalyst with many different substrates for the potential discovery of a new bond construction or a new catalyst for an existing bond construction

As demonstrated by the previous approaches to the use of high-throughput screening, most strategies focus on the discovery and optimization of a catalyst or reagent for a single chemical transformation. While this approach is very useful for reaction development and improvement, the ability to use a high-throughput approach for the discovery of a catalyst for a previously unknown chemical reaction would open up many new avenues of chemical reactivity. A pioneering study by Liu and co-workers applied DNA-templated synthesis and *in vitro* selection to evaluate many different substrates bearing a single functional group to discover new bond forming processes (Scheme 41).[82]

In this study, a small library of substrates containing a unique functional group tethered to a DNA fragment, split into two pools, was prepared. It was then hypothesized that upon mixing of these substrates in an aqueous solution, Watson-Crick pairing would occur to bring together each possible combination of the substrates in pool 1 with the substrates in pool 2. Following self-assembly in solution, exposure to a reagent or catalyst could result in an effectively intramolecular reaction between the functional groups on each of the two substrates. Following a standardized procedure involving Streptavidin affinity selection and DNA amplification with PCR, the two substrates that engaged in a bond forming process could be identified, and the potential new reaction could be identified through mass spectrometric analysis. In the first implementation of this system, after performing positive control experiments to identify EDC-mediated amide coupling and Cu(I) catalyzed Huisgen alkyne-azide cycloaddition, Liu and co-workers identified a Pd(II)-catalyzed coupling of an alkene and an alkyne to form a *trans*-enone. This approach to reaction discovery was later adopted for use in organic solvents, and a gold-catalyzed (or acid-catalyzed) alkene hydroarylation with indoles was discovered.[83]



Scheme 41. Use of DNA-templated synthesis for discovery of new bond forming reactions

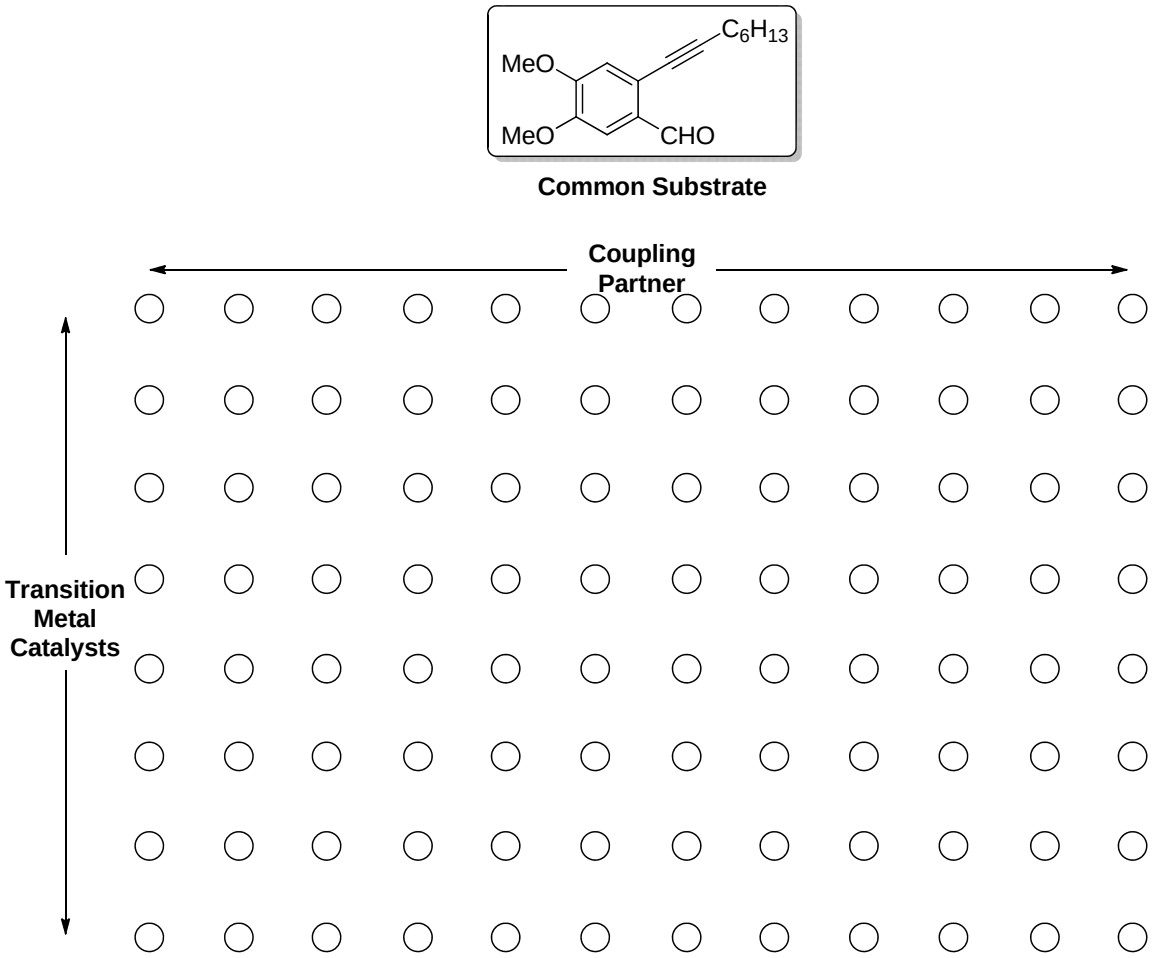
While this approach to reaction discovery based upon DNA-templated synthesis represents a tremendous development in the high-throughput screening of catalysts to discover new reactions, there are several limitations to this system. First, each DNA-linked substrate must be independently prepared, which is a laborious and time-consuming process. Second, it is not clear whether this system can tolerate transition metal catalysts that can be deactivated or "poisoned" by the DNA fragments present on each of the substrates. While most of the catalysts examined thus far are generally robust, such as Pd(II) or Au(III) salts, many useful transformations are catalyzed by water-sensitive or air-sensitive catalysts. Sensitive organometallic complexes have not been

investigated with this approach to reaction discovery and it is unclear what interaction, if any, would occur between these complexes, the DNA fragments which are a crucial element of the substrate, and the aqueous solvent, which is needed in this system. Last, this approach allows for examination of a single catalyst in each experiment.

2.3.3. Examination of many catalysts and many organic substrates for the potential discovery of new catalysts and new bond construction strategies

The examination of many catalysts for many different potential bond-forming reactions presents another opportunity to apply high-throughput screening to discover new chemical transformations. An innovative approach to this goal was demonstrated by Porco and co-workers. In their investigations, a molecular scaffold was selected that was known to undergo a certain class of reaction and known to react with a certain type of coupling partner, such as a nucleophiles or electrophile. Transition metal complexes were then examined for their ability to promote this process. The initial application of this approach was to the discovery of new catalysts to promote reactions with an *ortho*-alkynylbenzaldehyde (Scheme 42).[84] This substructure was previously known to undergo a variety of transition metal-catalyzed processes, such as cycloaddition reactions or cycloisomerization reactions. Therefore, Porco and co-workers reasoned that this structure should be amenable to a variety of metal-catalyzed processes with electrophiles, nucleophiles and cycloaddition partners. To implement this reaction discovery approach, they mixed an *ortho*-alkynylbenzaldhyde with a variety of nucleophiles, such as malonates, nucleophilic (hetero)arenes and alcohols, electrophiles, such as epoxides and enals, and cycloaddition partners, such as dienes and phthalimides. These binary combinations of substrates were then exposed systematically to a single transition metal

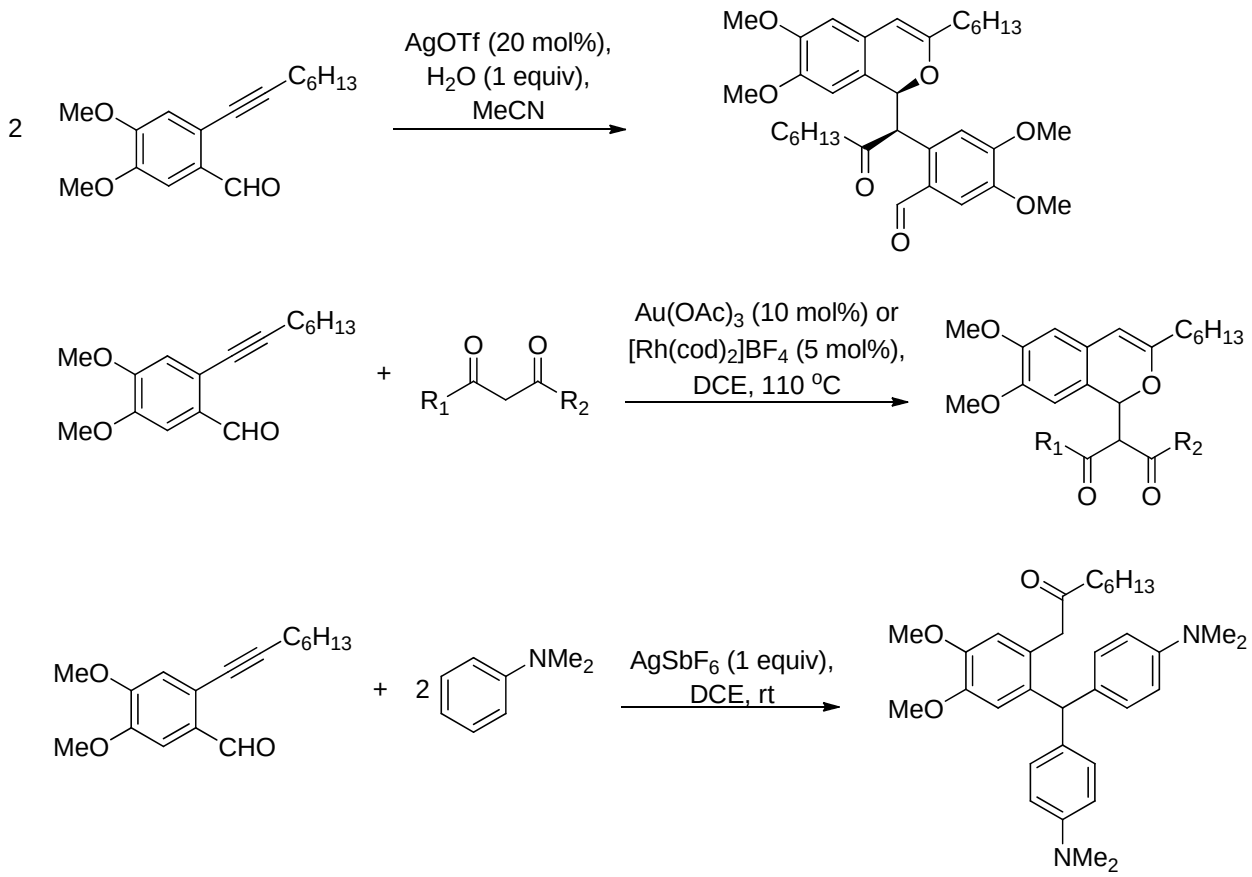
catalyst. The array of reactions was then heated, and assayed by LC/MS/ELSD. If a new species in a significant quantity was observed in the LC trace, then the reaction was repeated on a larger scale and the product was identified through standard spectroscopic and computational techniques.



Scheme 42. Multidimensional reaction discovery with *ortho*-alkynylbenzaldehydes

Porco and co-workers were able to discover several new transformations of *ortho*-alkynylbenzaldehydes. These new transformations include silver-catalyzed dimerization of the *ortho*-alkynylbenzaldehyde, gold-catalyzed or rhodium-catalyzed cycloisomerization/addition of 1,3-dicarbonyl compounds, and silver-catalyzed or platinum-catalyzed cycloisomerization/Friedel-Crafts addition (Scheme 43). All of these

transformations could be scaled to a mmol-scale reaction with high reaction yield. While all of these reactions are based on a single framework, many of them could not have been predicted *de novo*, highlighting the utility of this approach to reaction discovery. This technique has been extended to a variety of other applications, including identification of tandem processes based upon nucleophilic additions to imines,[85] derivatization of a natural product scaffold,[86] and extension to reaction screening and discovery in a flow reactor.[87-88] While this strategy for reaction and catalyst discovery has yielded interesting results, because these reactions are based on a single central structure, the broad utility of the transformations discovered with this approach is inherently limited. Future applications where this limitation can be overcome will broaden the utility of multi-dimensional reaction discovery.



Scheme 43. New transition metal-catalyzed transformations of *ortho*-alkynylbenzaldehydes discovered via catalyst screening

2.4 Summary and Objectives

This review encompasses many of the major developments in the application of high-throughput screening to the discovery and development of transition metal catalysts. Although combinatorial approaches to catalyst discovery have only begun to be broadly embraced recently, advances in the technology for the use of high-throughput catalyst screening has already had a significant impact on how catalysts are developed in both academic and industrial settings. These developments are likely to continue in the future, especially as the specialized technology used for screening and reaction analysis becomes available to more laboratories. Chapter 6 will describe the invention and development of

a new, simple reaction discovery based on multidimensional screening of transition metal catalysts, and the application of this system to the discovery of several new transition metal-catalyzed transformations of simple organic substrates.

2.5 References

(1) J. F. Hartwig. Organotransition Metal Chemistry: From Bonding to Catalysis`, University Science Books`, Sausalito`, 2010.

(2) King, A. O.; Yasuda, N. In T*opics in Organometallic Chemistry;* Springer Berlin / Heidelberg: 2004; Vol. 6, p 205.

(3) McQuade, D. T.; Pullen, A. E.; Swager, T. M. C*hem. Rev.* 2**000,** 1*00,* 2537.

(4) Thomas, S. W.; Joly, G. D.; Swager, T. M. C*hem. Rev.* 2**007,** 1*07,* 1339.

(5) Cook, T. R.; Dogutan, D. K.; Reece, S. Y.; Surendranath, Y.; Teets, T. S.; Nocera, D. G. C*hem. Rev.* 2**010,** 1*10,* 6474.

(6) Esswein, A. J.; Nocera, D. G. C*hem. Rev.* 2**007,** 1*07,* 4022.

(7) Howard`, P.`; Morris`, G.`; Sunley`, G. in "Metal-Catalysis in Industrial Organic Processes." Royal Society of Chemistry`, Cambridge`, UK`, 2006`, p. 1-22.

(8) Wender, P. A.; Croatt, M. P.; Witulski, B. T*etrahedron* 2**006,** 6*2,* 7505.

(9) Wender`, P. A.`; Baryza`, J. L.`; Brenner`, S. E.`; Clarke`, M. O.`; Gamber`, G. G.`; Horan`, J. C.`; Jessop`, T. C.`; Kan`, C.`; Pattabiraman`, K.`; Williams`, T. J. Pure Appl. Chem.`, 2003`, 75`, 143-156.

(10) Wender, P. A.; Snapper, M. L. T*etrahedron Lett.* 1**987,** 2*8,* 2221.

(11) Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. O*rg. Lett.* 1**999,** 1, 137.

(12) Heck, R. F. J. *Am. Chem. Soc.* 1**969,** *91,* 6707.

(13) Heck, R. F.; Nolley, J. P. J. *Org. Chem.* 1**972,** *37,* 2320.

(14) Mizoroki, T.; Mori, K.; Ozaki, A. B*ull. Chem. Soc. Jpn.* 1**971,** 4*4,* 581.

(15) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. J. *Am. Chem. Soc.* 2**001,** 1*23,* 2677.

(16) Yao, Q.; Kinney, E. P.; Yang, Z. J. *Org. Chem.* 2**003,** 6*8,* 7528.

(17) Littke, A. F.; Fu, G. C. J. *Org. Chem.* 1**998,** 6*4,* 10.

(18) de Vries, J. G. C*an. J. Chem.* 2**001,** 7*9,* 1086.

(19) Jacobsen, E. N.; Breinbauer, R. S*cience* 2**000,** 2*87,* 437.

(20) Eleuterio, H. S. J. *Mol. Catal.* 1**991,** 6*5,* 55.

(21) Furstner, A. C*hem. Commun.* 2**011,** 4*7,* 6505.

(22) Hoveyda, A. H.; Zhugralin, A. R. N*ature* 2**007,** 4*50,* 243.

(23) Sanford, M. S.; Love, J. A.; Grubbs, R. H. J. *Am. Chem. Soc.* 2**001,** 1*23,* 6543.

(24) Jean-Louis Hérisson, P.; Chauvin, Y. M*akromol. Chem.* 1**971,** 1*41,* 161.

(25) Grubbs, R. H. A*ngew. Chem. Int. Ed.* 2**006,** 4*5,* 3760.

(26) Chauvin, Y. A*ngew. Chem. Int. Ed.* 2**006,** 4*5,* 3740.

(27) Schrock, R. R. A*ngew. Chem. Int. Ed.* 2**006,** 4*5,* 3748.

(28) Liu, D. R.; Schultz, P. G. A*ngew. Chem. Int. Ed.* 1**999,** 3*8,* 36.

(29) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. P*roc. Nat. Acad. Sci.* 1**994,** *91,* 4708.

(30) Danielson, E.; Golden, J. H.; McFarland, E. W.; Reaves, C. M.; Weinberg, W. H.; Wu, X. D. N*ature* 1**997,** 3*89,* 944.

(31) Reddington, E.; Sapienza, A.; Gurau, B.; Viswanathan, R.; Sarangapani, S.; Smotkin, E. S.; Mallouk, T. E. S*cience* 1**998,** 2*80,* 1735.

(32) Briceño, G.; Chang, H.; Sun, X.; Schultz, P. G.; Xiang, X.-D. S*cience* 1**995,** 2*70,* 273.

(33) Maier, W. F.; Stöwe, K.; Sieg, S. A*ngew. Chem. Int. Ed.* 2**007,** 4*6,* 6016.

(34) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. C*urr. Opin. Chem. Biol.* 1**998,** 2*,* 422.

(35) Stambuli, J. P.; Hartwig, J. F. C*urr. Opin. Chem. Biol.* 2**003,** 7*,* 420.

(36) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. A*ngew. Chem. Int. Ed. Engl.* 1**996,** 3*5,* 1668.

(37) Sigman, M. S.; Jacobsen, E. N. J. *Am. Chem. Soc.* 1**998,** 1*20,* 4901.

(38) Doyle, A. G.; Jacobsen, E. N. C*hem. Rev.* 2**007,** 1*07,* 5713.

(39) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. A*ngew. Chem. Int. Ed.* 2**002,** 4*1,* 1009.

(40) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. J. *Am. Chem. Soc.* 2**001,** 1*23,* 11594.

(41) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. J. *Am. Chem. Soc.* 2**000,** 1*22,* 2657.

(42) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. J. *Am. Chem. Soc.* 1**999,** 1*21,* 4284.

(43) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. J. *Am. Chem. Soc.* 2**001,** 1*23,* 755.

(44) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. A*ngew. Chem. Int. Ed.Engl.* 1**996,** 3*5,* 220.

(45) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. J. *Am. Chem. Soc.* 2**000,** 1*22,* 5043.

(46) Boussie, T. R.; Coutard, C.; Turner, H.; Murphy, V.; Powers, T. S. A*ngew. Chem. Int. Ed.* 1**998,** 3*7,* 3272.

(47) Boussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M.; Lund, C.; Murphy, V.; Shoemaker, J. A. W.; Tracht, U.; Turner, H.; Zhang, J.; Uno, T.; Rosen, R. K.; Stevens, J. C. J. *Am. Chem. Soc.* 2**003,** 1*25,* 4306.

(48) Chen, P. A*ngew. Chem. Int. Ed.* 2**003,** 4*2,* 2832.

(49) Reetz, M. T. A*ngew. Chem. Int. Ed.* 2**008,** 4*7,* 2556.

(50) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. A*ngew. Chem. Int. Ed.* 2**003,** 4*2,* 790.

(51) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. O*rg. Lett.* 2**003,** 5, 3111.

(52) Reetz, M. T.; Li, X. A*ngew. Chem. Int. Ed.* 2**005,** 4*4,* 2962.

(53) Reetz, M. T.; Bondarev, O. A*ngew. Chem. Int. Ed.* 2**007,** 4*6,* 4523.

(54) Breit`, B. Pure Appl. Chem.`, 2008`, 80`, 855-860

(55) Breit, B.; Seiche, W. J. *Am. Chem. Soc.* 2**003,** 1*25,* 6608.

(56) de Greef, M.; Breit, B. A*ngew. Chem. Int. Ed.* 2**009,** 4*8,* 551.

(57) Wieland, J.; Breit, B. N*at Chem* 2**010,** 2, 832.

(58) Sandee, A. J.; Reek, J. N. H. D*alton Trans.* 2**006,** 3385.

(59) Jäkel, C.; Paciello, R. C*hem. Rev.* 2**006,** 1*06,* 2912.

(60) Roseblade, S. J.; Pfaltz, A. A*cc. Chem. Res.* 2**007,** 4*0,* 1402.

(61) Shultz, C. S.; Krska, S. W. A*cc. Chem. Res.* 2**007,** 4*0,* 1320.

(62) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. J. *Am. Chem. Soc.* 2**001,** 1*23,* 4641.

(63) Stauffer, S. R.; Hartwig, J. F. J. *Am. Chem. Soc.* 2**003,** 1*25,* 6977.

(64) Littke, A. F.; Fu, G. C. J. *Am. Chem. Soc.* 2**001,** 1*23,* 6989.

(65) Miller, S. J. A*cc. Chem. Res.* 2**004,** 3*7,* 601.

(66) Copeland, G. T.; Miller, S. J. J. *Am. Chem.Soc.* 2**001,** 1*23,* 6496.

(67) Lewis, C. A.; Miller, S. J. A*ngew. Chem. Int. Ed.* 2**006,** 4*5,* 5616.

(68) Hinderling, C.; Chen, P. I*nt. J. Mass Spectrom.* 2**000,** 1*95-196,* 377.

(69) Dietiker, R.; Chen, P. A*ngew. Chem. Int. Ed.* 2**004,** 4*3,* 5513.

(70) Volland, M. A. O.; Adlhart, C.; Kiener, C. A.; Chen, P.; Hofmann, P. C*hem. Eur. J.* 2**001,** 7*,* 4621.

(71) Hinderling, C.; Feichtinger, D.; Plattner, D. A.; Chen, P. J. *Am. Chem. Soc.* 1**997,** 1*19,* 10793.

(72) Hinderling, C.; Chen, P. A*ngew. Chem. Int. Ed.* 1**999,** 3*8,* 2253.

(73) Feichtinger, D.; Plattner, D. A.; Chen, P. J. *Am. Chem. Soc.* 1**998,** 1*20,* 7125.

(74) Muller, C. A.; Markert, C.; Teichert, A. M.; Pfaltz, A. C*hem. Commun.* 2**009,** 1607.

(75) Markert, C.; Pfaltz, A. A*ngew. Chem. Int. Ed.* 2**004,** 4*3,* 2498.

(76) Teichert, A.; Pfaltz, A. A*ngew. Chem. Int. Ed.* 2**008,** 4*7,* 3360.

(77) Lavastre, O.; Morken, J. P. A*ngew. Chem. Int. Ed.* 1**999,** 3*8,* 3163.

(78) Löber, O.; Kawatsura, M.; Hartwig, J. F. J. *Am. Chem. Soc.* 2**001,** 1*23,* 4366.

(79) Evans, M. A.; Morken, J. P. J. *Am. Chem. Soc.* 2**002,** 1*24,* 9020.

(80) Reetz, M. T.; Eipper, A.; Tielmann, P.; Mynott, R. A*dv. Synth. Catal.* 2**002,** 3*44,* 1008.

(81) Taylor, S. J.; Morken, J. P. S*cience* 1**998,** 2*80,* 267.

(82) Kanan, M. W.; Rozenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. N*ature* 2**004,** 4*31,* 545.

(83) Rozenman, M. M.; Kanan, M. W.; Liu, D. R. J. *Am. Chem. Soc.* 2**007,** 1*29,* 14933.

(84) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A. J. *Am. Chem. Soc.* 2**007,** 1*29,* 1413.

(85) Kinoshita, H.; Ingham, O. J.; Ong, W. W.; Beeler, A. B.; Porco, J. A. J. *Am. Chem. Soc.* 2**010,** 1*32,* 6412.

(86) Balthaser, B. R.; Maloney, M. C.; Beeler, A. B.; Porco, J. A.; Snyder, J. K. N*at Chem* 2**011,** 3, 969.

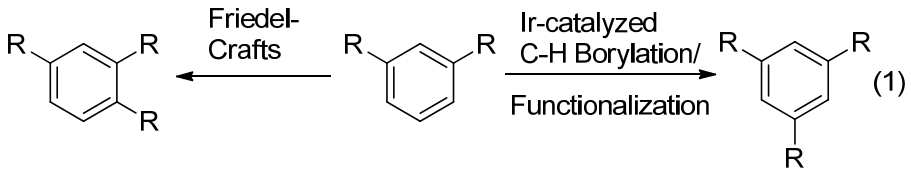
(87) Goodell, J. R.; McMullen, J. P.; Zaborenko, N.; Maloney, J. R.; Ho, C.-X.; Jensen, K. F.; Porco, J. A.; Beeler, A. B. J. *Org. Chem.* 2**009,** 7*4,* 6169.

(88) Treece, J. L.; Goodell, J. R.; Velde, D. V.; Porco, J. A.; Aubé, J. J. *Org. Chem.* 2**010,** 7*5,* 2028.

Chapter 3. Alkylation of Arenes with Steric Control via Iridium-Catalyzed C-H Borylation

3.1 Introduction

Selective functionalization of C-H bonds has significant potential to improve the efficiency of organic synthesis.[1] Because substituted arenes are key structures in bulk chemicals, polymeric materials and complex natural products and pharmaceuticals, methods for arene functionalization are particularly useful. Classical functionalizations of arenes that form carbon-carbon bonds are based on electrophilic aromatic substitution with carbon electrophiles (Friedel-Crafts Reactions). Because electronic effects generally control the site-selectivity of Friedel-Crafts reactions, arenes containing electron-donating groups undergo these processes, and the carbon-carbon bond is formed at the positions *ortho* and *para* to the donating groups (Equation 1). Arenes containing electron-withdrawing groups undergo reactions at positions *meta* to the substituents, but arenes with such substituents are significantly less reactive than those with electron-donating groups, and harsh reaction conditions are often needed for reactions of these electron-poor arenes.



The site-selectivity for formation of C-C bonds at aromatic systems can be controlled by transition metal-catalyzed chemistry. Cross-coupling reactions occur at a specific site, but these reactions require the arene to contain a halide or pseudohalide at the reactive site, and this group is installed by electrophilic aromatic substitution that is governed by the same effects as Friedel-Crafts reactions. Transition metal-catalyzed

functionalizations of aromatic C-H bonds have been studied extensively, but most of these reactions that form C-C bonds occur with a group on the arene that leads to reaction at the position *ortho* to this substituent.[2]

3.2 Background

The site-selectivity of iridium-catalyzed C-H borylation is predominantly controlled by steric factors that lead to borylation at the least hindered C-H bond (Equation 1).[3] Therefore, 1,3-disubstituted and 1,2,3-trisubstituted arenes yield 3,5-disubstituted and 3,4,5-trisubstituted arylboronate esters, respectively. In addition to the *meta*-selectivity of this C-H activation reaction, aryl pinacol boronate esters offer several advantages over other boron compounds, including stability to chromatography which allows for isolation, and stability to other synthetic processes. One of the significant challenges in the utilization iridium-catalyzed arene borylation to develop useful synthetic methods is the discovery and development of methods for functionalization of the pinacol boronate ester, which is significantly less reactive than other aryl boron species, such as aryl boronic acids or neopentyl boronate esters. *Meta*-selective arene borylation has been used to develop methods for the synthesis of aryl chlorides and bromides,[4] phenols,[5] boronic acids, potassium trifluoroborates,[6] nitriles,[7] aryl amines and ethers,[8] and perfluoroalkyl groups.[9]

Thus, a method to form C-C bonds in which the arene is linked to an sp^3-hybridized groups by a reaction with site selectivity that is governed by steric, rather than electronic or directing effects, would create new methods to form arenes with new substitution patterns. Methods for *meta*-arylation[10] and *meta*-olefination[11] have been developed recently, but these methods suffer from the need for a different type of

directing group, high catalyst loading, limited substrate scope, poor regioselectivity, or a need for a large excess of the arene substrate. We have developed a one-pot method for *meta*-selective alkylation of arenes by Ir-catalyzed C-H borylation, followed by Pd-catalyzed or Ni-catalyzed coupling of the resulting arylboronate ester with alkyl electrophiles. This transformation represents a general method for *meta*-selective Friedel-Crafts type arene alkylation with the site-selectivity controlled by steric effects as opposed to electronic effects.

3.3 Results and Discussion

We began our investigation by developing a method for the *meta*-selective allylation of arenes. The development of a method for *meta*-selective allylation of arenes required the development of a method to couple aryl pinacolboronates with allylic electrophiles. Several methods for the Pd-catalyzed coupling of organoboranes with allylic acetates, alcohols and halides have been developed.[12] These methods generally utilize a Pd(0) or Pd(II) catalyst precursor, phosphine ligand, and a basic additive, such as carbonate or fluoride. After surveying reaction conditions for the allylation of electron-rich and electron-deficient aryl boronate esters with cinnamyl acetate, $Pd(dba)_2$ with KF as an additive in MeOH solvent at room temperature was found to provide the *meta*-allylation products in good yield.[13]

Similar to the method for *meta*-allylation, a method for *meta*-benzylation of arenes was sought. Several methods for Pd-catalyzed coupling of organometallic reagents with benzylic electrophiles, including halides and phosphates, have been developed.[14] Direct benzylation of aromatic and heteroaromatic C-H bonds has also been developed, but these methods require either acidic C-H bonds or a directing group.[15] We

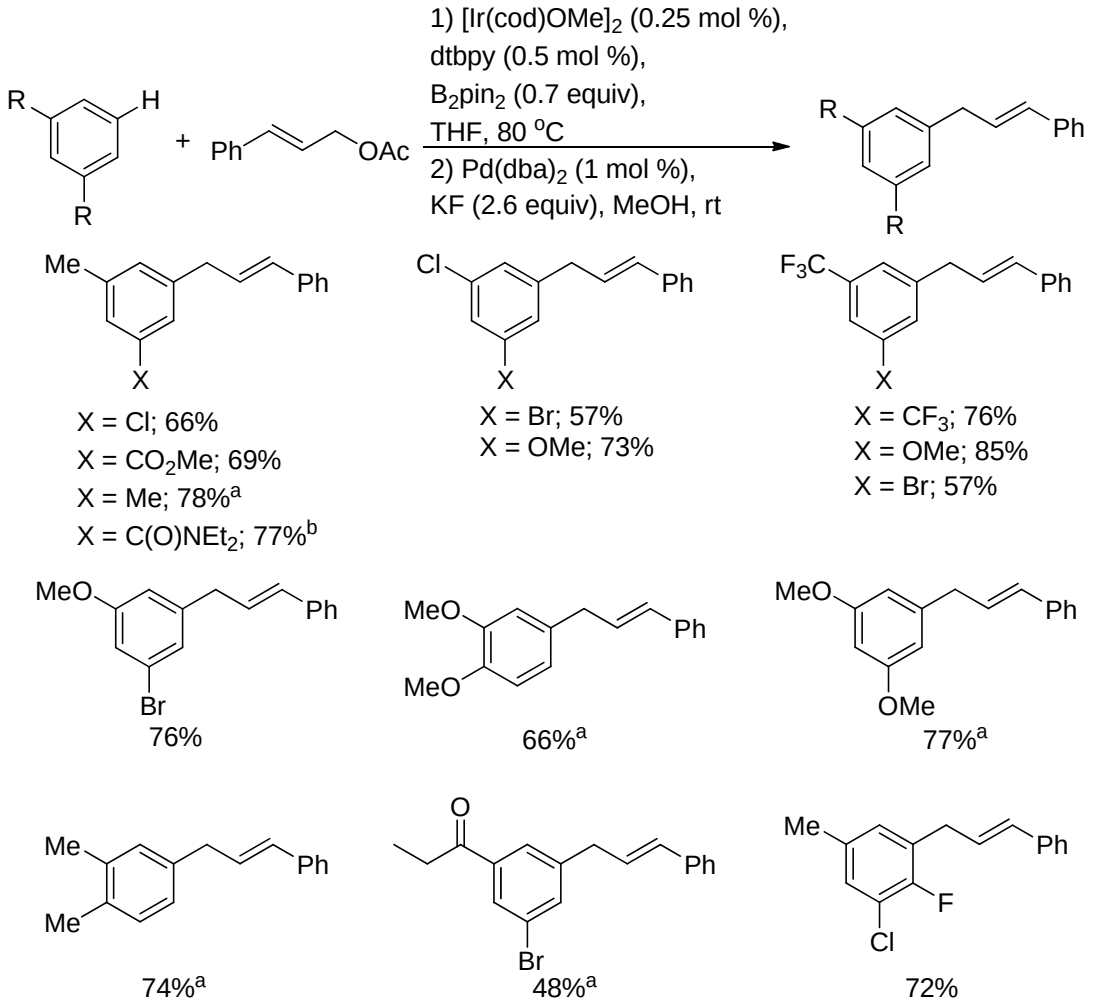
found that a catalyst formed *in situ* from the combination of $Pd(dba)_2$ and PPh_3 with Na_2CO_3 in a mixture of THF and H_2O at 100 °C provided good yields of the product from the coupling of electron-rich and electron-deficient aryl boronate esters with 4-methylbenzyl bromide.

With these methods for coupling of aryl boronate esters with cinnamyl acetate and 4-methylbenzyl bromide, we developed one-pot methods for *meta*-allylation and *meta*-benzylation of arenes. Reactions of 1,3-disubstituted arenes with bis(pinacolato)diboron in the presence of a catalyst formed *in situ* from the combination of $[Ir(cod)OMe]_2$ and 4,4'-di-*tert*-butylbipyridine (dtbpy) in THF at 80 °C, followed by addition of the appropriate Pd catalyst, the allylic or benzylic electrophile, additive and solvent gave good yield of the *meta*-allylation or *meta*-benzylation product.

After identification of these conditions, the scope of *meta*-allylation with 1,2-, or 1,3- substituted arenes for coupling with cinnamyl acetate was explored (Table 1). This methodology gives good yields of the *meta*-allylation products from electron-rich and electron-deficient arenes and tolerates a variety of functional groups, including aryl fluorides, chlorides and bromides, esters, amides, ketones, ethers, and trifluoromethyl groups. Tetrasubstituted arenes were also be synthesized from 1,2,4-trisubstituted arenes by borylation *ortho* to a fluorine substituent on the arene. *Meta*-benzylation also furnishes good yield for electron-rich and electron-deficient arenes and tolerates a variety of functional groups. The *meta*-benzylation methodology also tolerates heteroarenes, including benzothiophene and pyridine derivatives (Table 2). Alkylation of benzothiophene occurs at C-2, whereas the uncatalyzed addition of alkyl halides occurs at

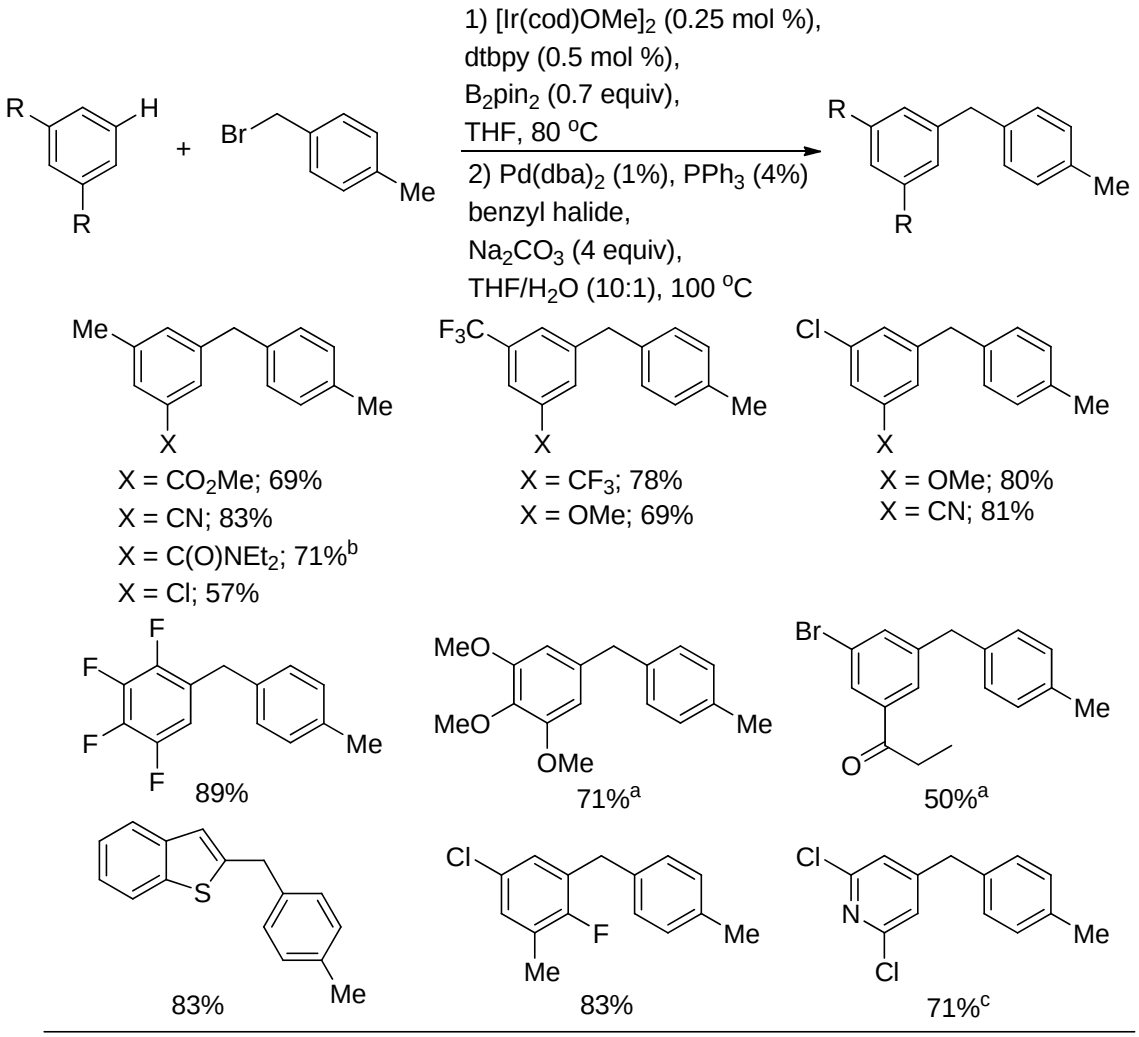
C-3, so the borylation-alkylation approach also gives orthogonal site-selectivity for the alkylation of heteroarenes.

Table 1. Scope of allylation of 1,3-disubstituted arenes with cinnamyl acetate



[a]Borylation conducted with 0.5 mol% $[Ir(cod)OMe]_2$ and 1.0 mol% dtbpy, [b]Borylation conducted with 1.0 mol% $[Ir(cod)OMe]_2$ and 2.0 mol% dtbpy

Table 2. Scope of benzylation of 1,3-disubstituted arenes with 4-methylbenzyl bromide



[a]Borylation conducted with 0.5 mol% $[Ir(cod)OMe]_2$ and 1.0 mol% dtbpy, [b]Borylation conducted with 1.0 mol% $[Ir(cod)OMe]_2$ and 2.0 mol% dtbpy; [c]Borylation conducted with 2.0 mol% $[Ir(cod)OMe]_2$ and 4.0 mol% dtbpy

These borylation-allylation and borylation-benzylation methodologies can also be applied to the regioselective allylation and benzylation of heteroarenes. The allylation of nitrogen, oxygen and sulfur heterocycles occurred in good overall yields (Table 3). Cinnamyl chloride was found to be a more effective allylic electrophile than cinnamyl acetate for the allylation of heteroarenes. The benzylation with 4-methylbenzyl bromide

also occurred with nitrogen, oxygen and sulfur heterocycles in good yield (Table 4). These allylation and benzylation methodologies give site-selectivity that is orthogonal to that of uncatalyzed electrophilic addition to the heterocycle in most cases. For example, the borylation of benzofuran and ethyl indole-2-carboxylate leads to functionalization at the 2-position and 7-position, whereas electrophilic addition would lead to functionalization at the 3-position of these heteroarenes.

Table 3. Scope of allylation of heterocycles with cinnamyl chloride

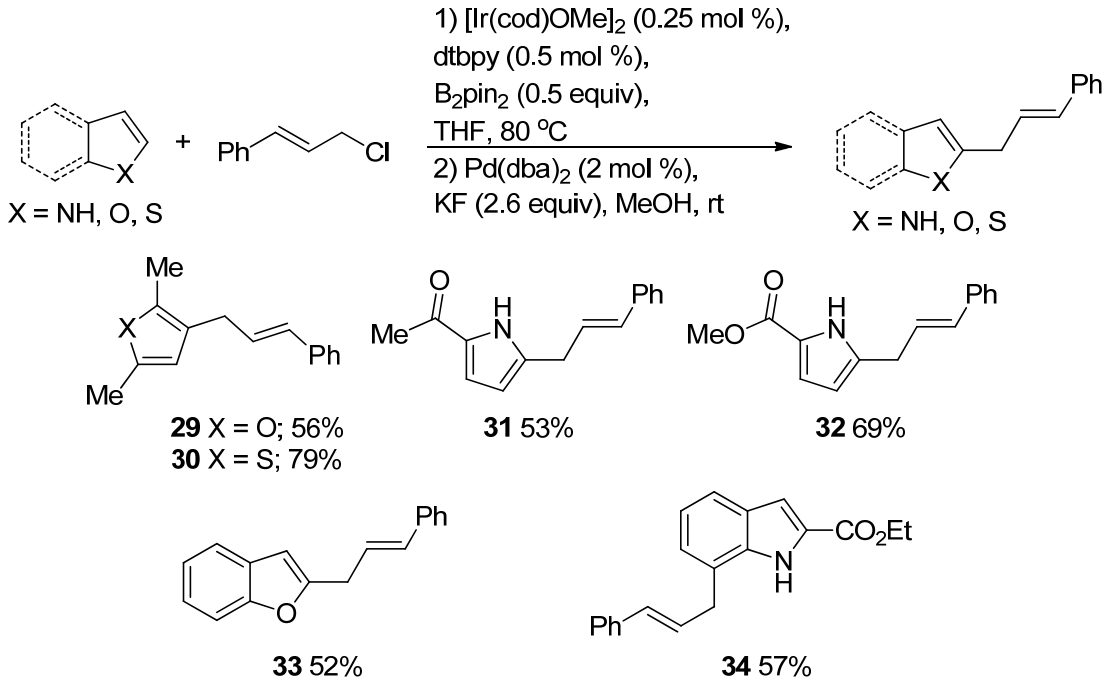
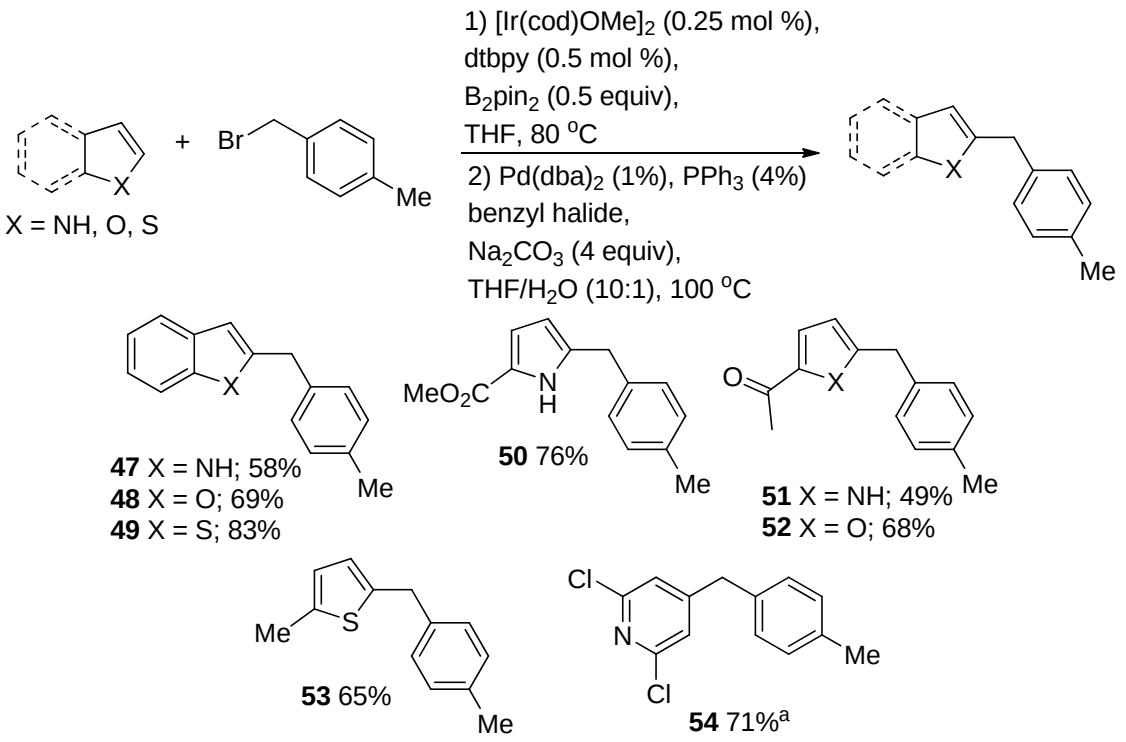
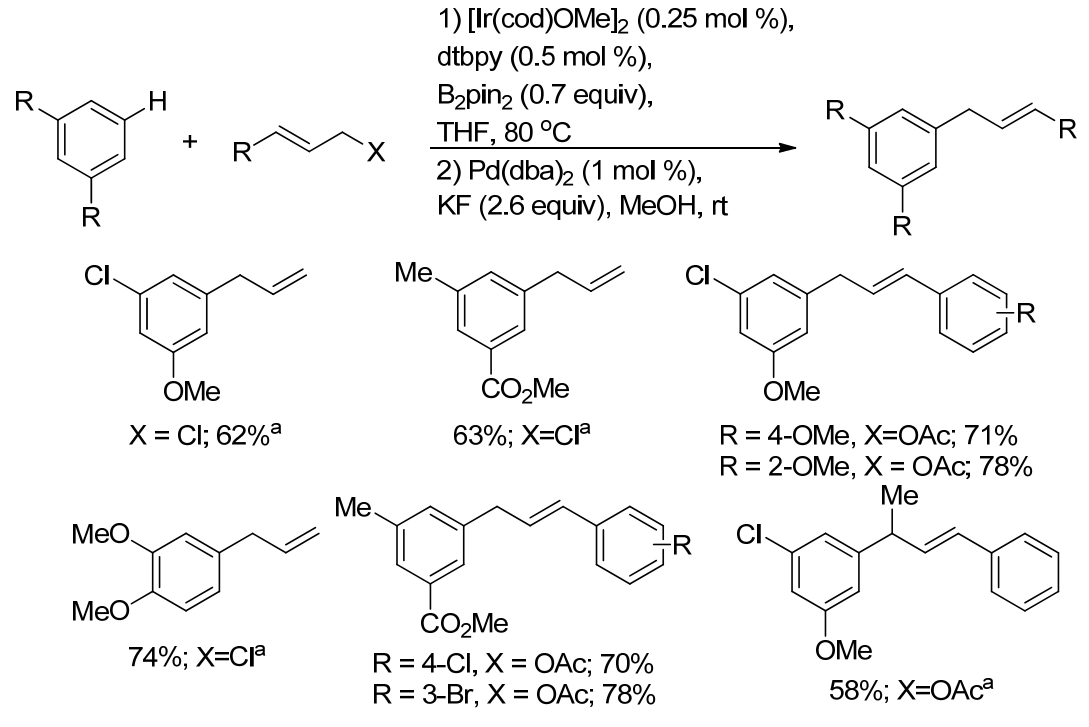


Table 4. Scope of benzylation of heteroarenes with 4-methylbenzyl bromide



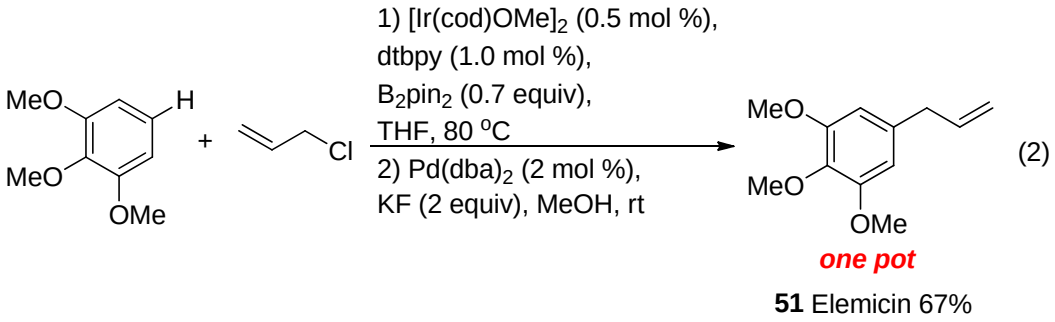
[a]Borylation conducted with 2.0 mol% $[Ir(cod)OMe]_2$ and 4.0 mol% dtbpy

Table 5. Scope of allylation with various allylic electrophiles



[a]Allylation conducted with 2 mol% $Pd(dba)_2$

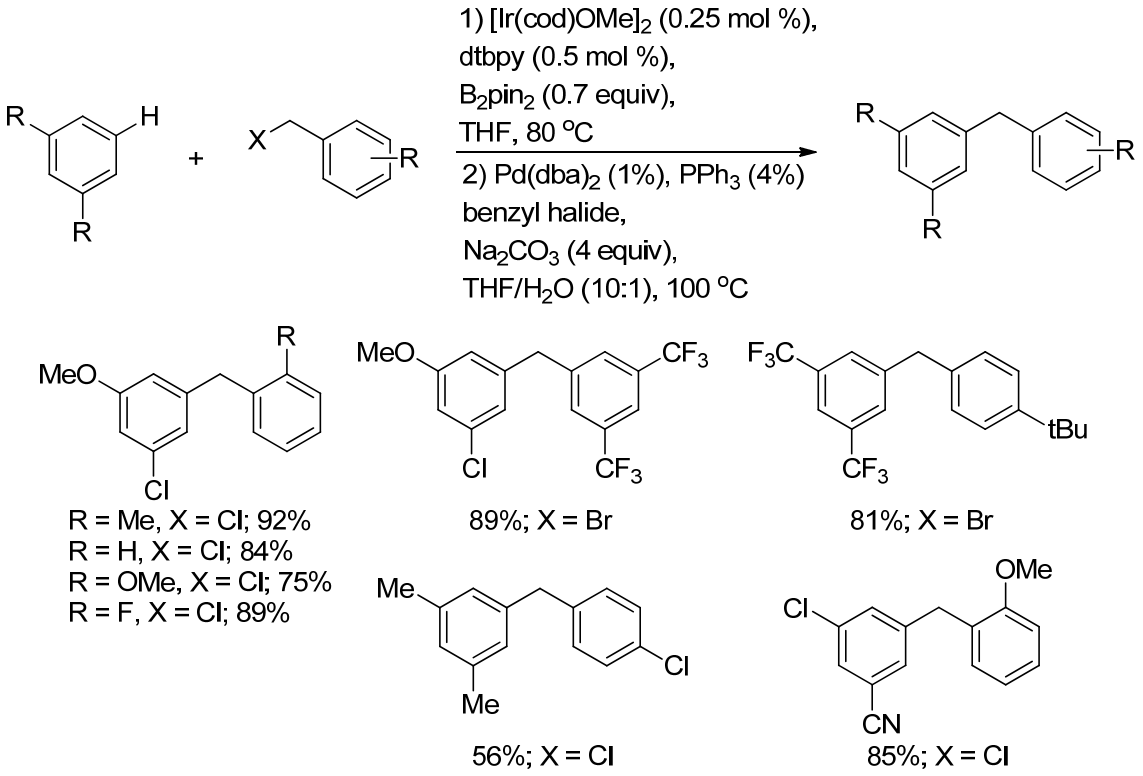
Several natural products contain a *meta*-allyl arene substructure. One such natural product, elemicin, has been synthesized in a one-pot borylation-allylation sequence (Equation 2). Elemicin has shown activity as a potential antibacterial agent.[17] These natural products have been synthesized previously by starting with prefunctionalized substrates, such as aryl halides or aryl boron compounds,[18] making this approach a more attractive synthesis because it was accomplished in a one-pot procedure from easily-obtained starting materials.



(2)

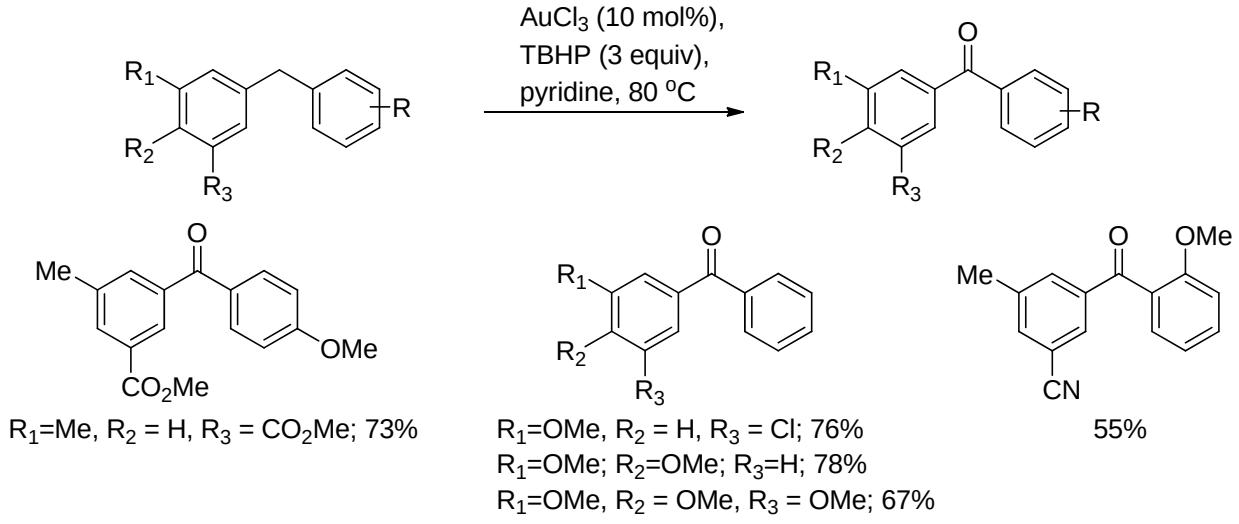
In addition to the coupling with 4-methylbenzyl bromide, the *meta*-selective borylation and benzylation was performed with a variety of benzyl halides (Table 6). Benzyl bromides and benzyl chlorides coupled with similar efficiency. Benzyl halides containing electron-donating groups, electron-withdrawing groups and *ortho*-substituents all reacted in good yield.

Table 6. Scope of *meta*-benzylation with various benzyl bromides and chlorides



After a general method for *meta*-selective benzylation of arenes had been developed, we sought to extend this methodology to the equivalent of a *meta*-acylation of arenes. This transformation could be effected by the *meta*-benzylation of an arene, followed by oxidation of the resulting diarylmethane to a diarylketone. After a survey of various oxidation conditions, we found that treatment of the diarylmethane with $AuCl_3$ and *tert*-butylhydroperoxide in pyridine at 80 °C provided good yield of a variety of diarylketone products (Table 7).[19] This oxidation methodology furnished substituted benzophenones in good yield from both electron-rich and electron-deficient arenes.

Table 7. Scope of oxidation of diarylmethanes to diarylketones

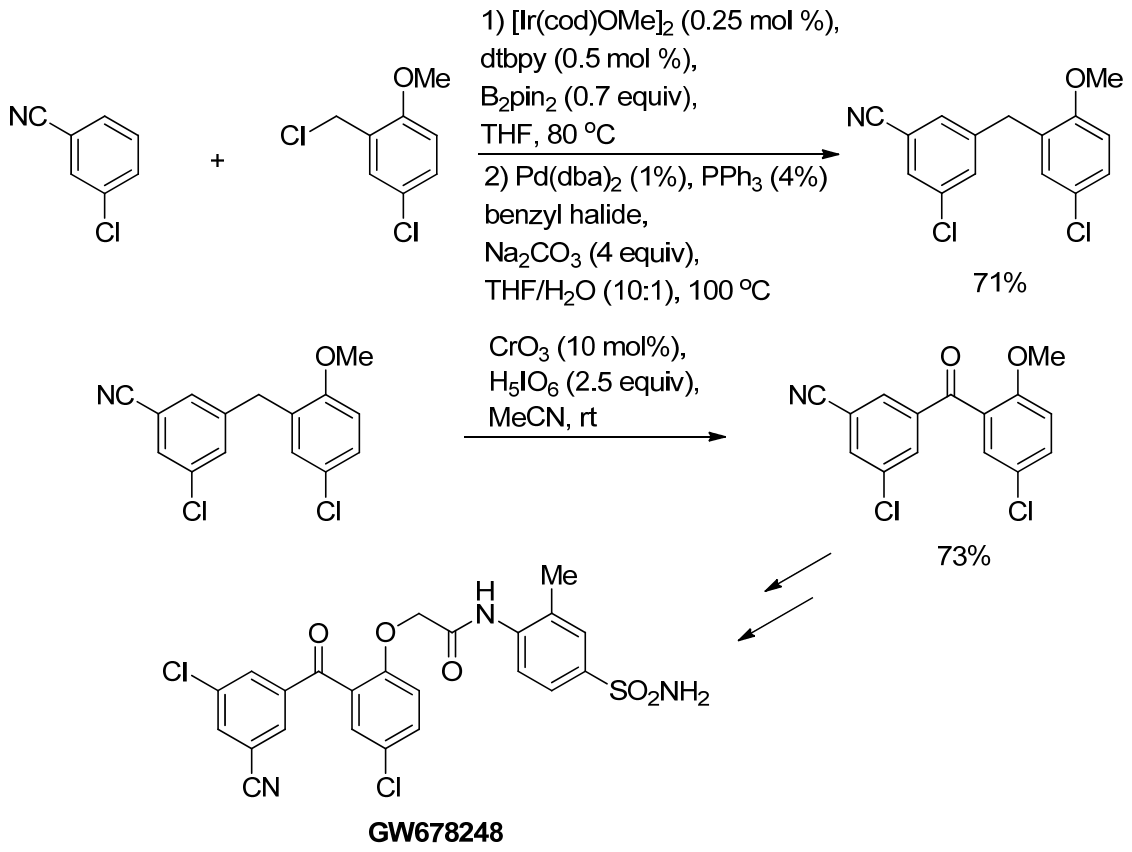


R_1=Me, R_2 = H, R_3 = CO_2Me; 73%

R_1=OMe, R_2 = H, R_3 = Cl; 76%
R_1=OMe; R_2=OMe; R_3=H; 78%
R_1=OMe, R_2 = OMe, R_3 = OMe; 67%

55%

This *meta*-benzylation and oxidation methodology was applied to the synthesis of a key intermediate in the production of a non-nucleotide reverse transcriptase inhibitor (NNRTI). A recent class of NNRTIs with a benzophenone core structure has recently been discovered and is in clinical development (Scheme 44).[20] *Meta*-benzylation of 3-chlorobenzonitrile with the appropriate benzyl halide provided the tetrasubstituted diarylmethane in 71% yield. The benzyl halide is readily synthesized from the corresponding methyl ester in two steps. In this case, oxidation of the diarylmethane to the diarylketone with a catalytic quantity of CrO_3 with periodic acid[21] as the terminal oxidant provided the substituted benzophenone. This ketone is a known intermediate in the synthesis of the final drug candidate in two steps.



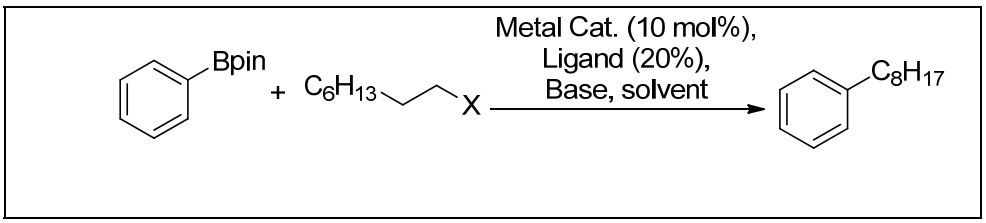
Scheme 44. Synthesis of NNRTI drug candidate via *meta*-benzylation and oxidation

While *meta*-selective introduction of allyl and benzyl groups yields useful products, a method for the introduction of other alkyl groups to an arene with steric control would significantly increase the scope of this transformation. This methodology requires a method for the coupling of aryl pinacol boronates with unactivated alkyl halides. For this coupling, palladium catalysts are generally less effective due to slow oxidative addition and β-hydride elimination from the Pd-alkyl complex formed after oxidative addition. To address these challenges, nickel[22] and copper[23] catalysts have been developed for Suzuki coupling with alkyl halides or pseudohalides.[24] The method for copper-catalyzed alkylation reported only a single example. Methods for nickel-catalyzed alkylation have generally utilized boronic acids or aryl 9-BBN-derivatives. Because

transmetallation have been proposed to be the rate-limiting step in nickel-catalyzed cross-coupling with alkyl halides, it was unclear whether the generally less-reactive pinacol boronate esters would participate in this transformation.[25] With these methods as a starting point, we sought to develop a general method for the coupling of aryl pinacol boronates with alkyl halides.

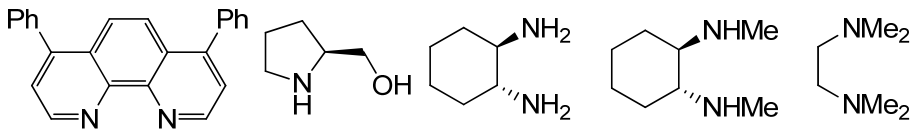
We initiated this study by examining various copper and nickel catalysts for the coupling of phenyl pinacol boronate with alkyl electrophiles. We examined various copper and nickel catalysts with 1-iodooctane or 1-octyl *p*-toluenesulfonate (Table 8). For reactions utilizing copper catalysts, we employed LiO*t*Bu as a base in DMF solvent. For reactions with nickel catalysts, KO*t*Bu was used with 2-butanol in dioxane solvent. We found that the best yield of 1-phenyloctane was obtained in the coupling of phenyl pinacol boronate ester with 1-iodooctane when $NiBr_2$-dme was used as the precatalyst with *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as the ancillary ligand.[22e] 1-bromooctane could also be utilized as the electrophile, albeit in lower yield. However, the yield could be increased by addition of NaI.

Table 8. Optimization of catalyst and reaction conditions for alkylation of aryl pinacol boronate esters



Entry	Catalyst	Ligand	X	Yield
1	CuI	None	OTs	44%
2	CuI	PPh_3	OTs	57%
3[a]	CuI	1,10-phen	OTs	32%
4	$Ni(cod)_2$	L1	I	44%
5[b]	$NiCl_2$-dme	L2	I	26%
6	$NiCl_2$-dme	L3	I	44%
7	$NiCl_2$-dme	L4	I	58%
8	$NiCl_2$-dme	L5	I	27%
9	$NiBr_2$-dme	L4	I	68%
10	$NiBr_2$-dme	L4	Br	55%
11[c]	$NiBr_2$-dme	L4	Br	69%

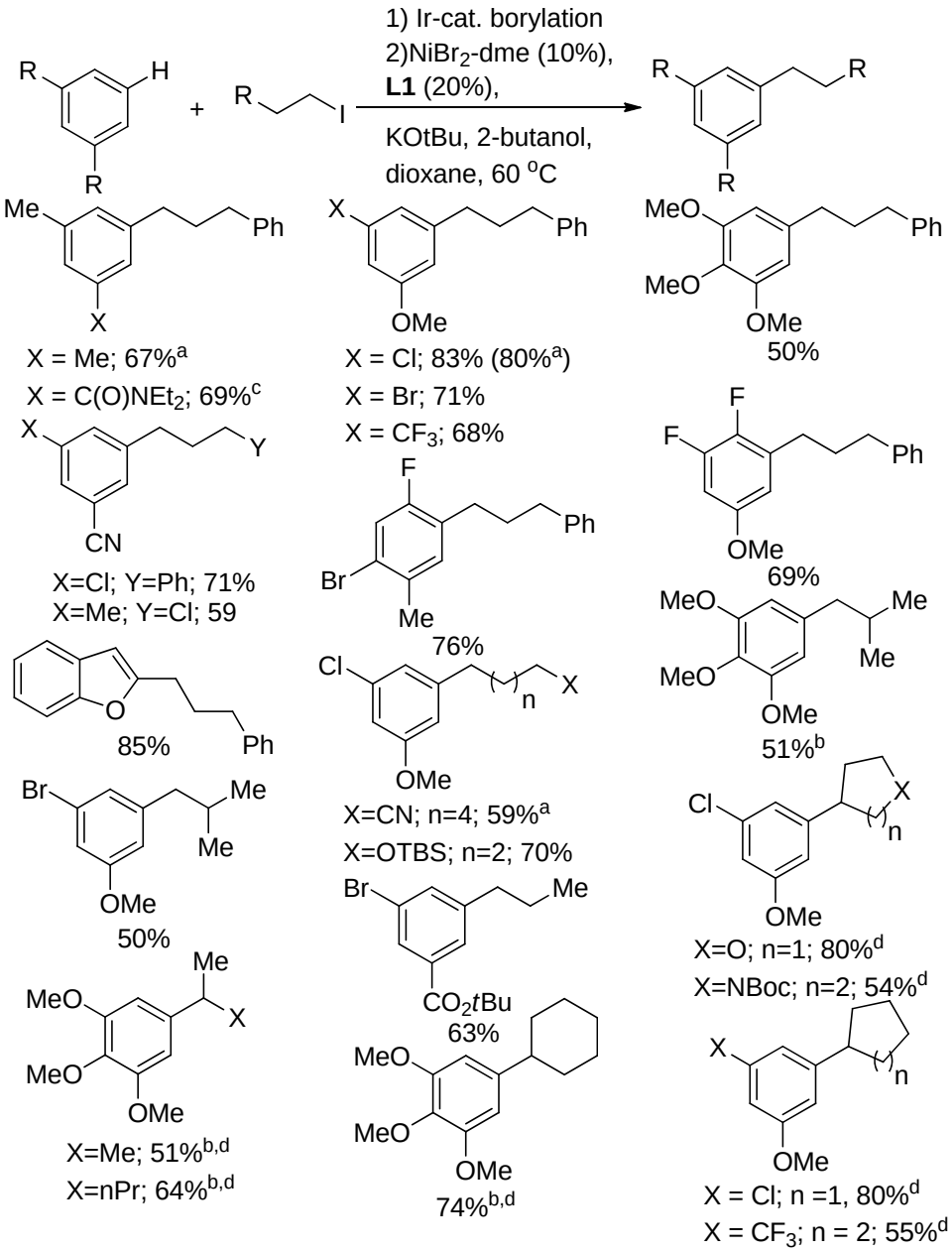
Yield determined by GC with an internal standard; [a] 10 mol% ligand used; [b]KHMDS (1.2 equiv) used as the base; [c]NaI (1 equiv) added



L1 **L2** **L3** **L4** **L5**

The scope of meta-selective alkylation with unactivated alkyl halides is shown in Table 9. Arenes with a variety of substituents were well tolerated, including ethers, aryl halides, nitriles, amides and trifluoromethyl groups. Arene borylation could be conducted *ortho* to fluorine and at the 2-position of benzofused heteroarenes, and these *ortho*-fluoropinacol boronates and heteroaryl pinacol boronates could be coupled with alkyl iodides in good yield, despite their increased propensity for protodeborylation in the context of other Suzuki coupling processes.[26] Primary alkyl iodides were utilized for the *meta*-selective alkylation, and primary alkyl bromides were utilized with addition of NaI, presumably to initiate halogen exchange, followed by coupling of the in situ generated alkyl iodide with the aryl pinacol boronate ester. Alkyl iodides with alkyl branching at the β-position were also tolerated.

Table 9. Scope of alkylation with unactivated alkyl electrophiles



[a]Alkylation conducted with alkyl bromide and NaI; [b]Borylation conducted with 0.5 mol% $[Ir(cod)OMe]_2$ and 1.0 mol% dtbpy; [c]Borylation conducted with 1.0 mol% $[Ir(cod)OMe]_2$ and 2.0 mol% dtbpy; [d]Alkylation reaction conducted with L1 in place of L4

When we attempted to apply these reaction conditions to *meta*-selective alkylation of arenes with secondary alkyl halides, low conversion and low yield of the alkylation

product was observed. We reexamined the catalyst used for this coupling reaction with secondary alkyl iodides, and found that increased yields were obtained when L1 was utilized as the ancillary ligand in combination with $NiBr_2$-dme in place of L4. With L4 as the ancillary ligand, secondary alkyl iodides could be employed as the alkyl electrophile in good yield (Table 9).

3.4 Conclusion and Outlook

In conclusion, a general method for the regioselective alkylation of arenes via Ir-catalyzed borylation and Pd- or Ni-catalyzed coupling has been developed. This method has a high tolerance for functional groups and occurs with various allylic, benzylic and unactivated aliphatic electrophiles. These arene functionalizations give products with regioselectivity that is complementary to directed C-H functionalization methods or C-H functionalization methods in which the regioselectivity is governed by electronic effects. The *meta*-allylation methodology has been used to perform a one-pot synthesis of a natural product, and the *meta*-benzylation has been used to perform *meta*-selective arene acylation via oxidation of the diarylmethane products, including the use of this sequence as a formal synthesis of an HIV drug candidate.

Future investigations will focus on the development of other useful and general regioselective functionalizations of arenes via iridium-catalyzed C-H borylation. As demonstrated in the two-pot method developed for *meta*-selective acylation of arenes, a direct method for this transformation has not been developed. Several classes of *meta*-acylation reactions are desireable, including methods for the synthesis of diarylketones, aryl-alkyl ketones, aryl amides and aryl esters. To begin to address this goal, we have developed conditions for the *meta*-selective amidation of arenes by a sequence of Ir-

catalyzed C-H borylation followed by palladium-catalyzed cross-coupling of the resulting pinacol boronate ester with a carbamoyl chloride (Table 10).

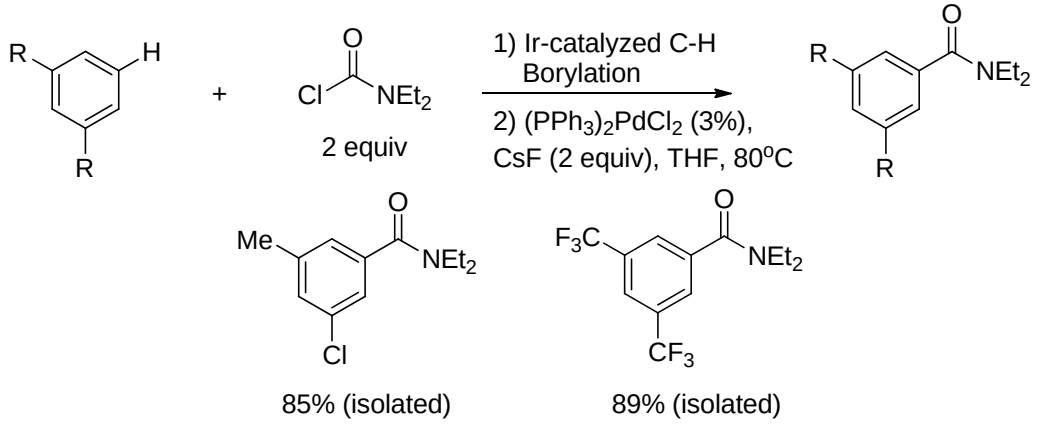


Table 10. *Meta*-selective amidation of arenes via iridium-catalyze C-H borylation followed by palladium-catalyzed coupling with a carbamoyl chloride

Future investigations will lead to other methods for *meta*-functionalization of arenes via C-H borylation. These methods will contribute solutions to unsolved problems in the synthetic methodology and will likely find utility in complex molecule synthesis.

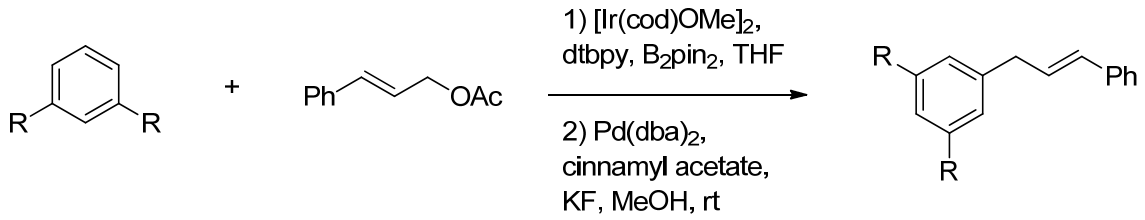
3.5 Experimental Information

General Procedures. All reactions were conducted under an argon or nitrogen atmosphere in flame-dried glassware or in an Innovative Technologies drybox. Dry and degassed solvents were used unless otherwise noted. Column chromatography was performed with a Teledyne Isco Combiflash® R_f system with Redi*Sep* R_f columns. Analytical thin-layer chromatography was performed on glass plates coated with silica gel (Silicycle, 60 A pore size, 40-64 um particle size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by ultraviolet light and staining solution of *p*-anisaldehyde or $KMnO_4$.

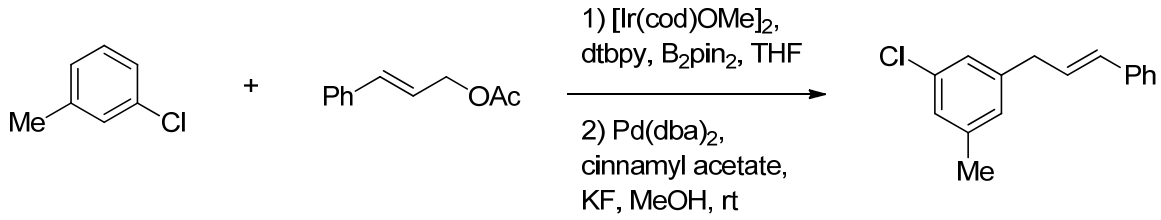
Materials. $[Ir(cod)OMe]_2$ was obtained from Johnson Matthey and used as received. 4,4'-di-*tert*-butylbipyridine, $NiCl_2$-dme, $NiBr_2$-dme, *trans*-cyclohexane-1,2-diamine, *trans*-*N*,*N*′-Dimethylcyclohexane-1,2-diamine, *S*-prolinol, TMEDA, 1,10-phenanthroline, 2-butanol, dry 1,4-dioxane, LiOtBu and KOtBu were obtained from Aldrich Chemicals and used as received. B_2pin_2 was obtained from Allychem and used as received. Arenes, heteroarenes, cinnamyl acetate, cinnamyl chloride, benzyl halides, allyl chloride, alkyl halides, triphenylphosphine, sodium carbonate, TBHP, H_5IO_6, CrO_3 and pyridine were obtained from Aldrich, Alfa Aesar, Acros or TCI America and used as received. Allylic electrophiles that were not commercially available were synthesized from the corresponding cinnamic acid derivative by reduction with DIBAL and acylation of the resulting alcohol with acetic anhydride. KF was obtained from Alfa Aesar and used as received. NaI was obtained from Fisher Scientific and used as received. $AuCl_3$, CuI, $Ni(cod)_2$, and bathophenanthroline were obtained from Strem Chemicals and used as received. $Pd(dba)_2$ was synthesized according to literature precedent.[27]

Instruments. ^{1}H NMR spectra were recorded on a 500 MHz Varian instrument (126 MHz for ^{13}C). Chemical shifts are reported in parts per million relative to residual protiated solvent (7.26 ppm for $CDCl_3$). GC-MS data were obtained on an Agilient 6890-N GC system containing an Alltech EC-1 capillary column and an Agilient 5973 mass selective detector.

Experimental Procedures

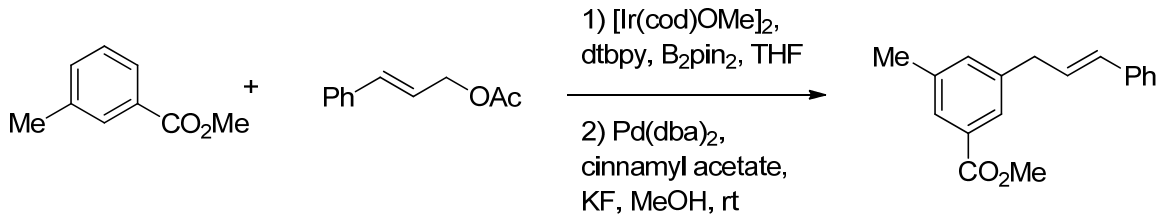


General Procedure for Allylation of Arenes. Inside a glove box, $[Ir(cod)OMe]_2$ (2.1 mg, 0.0033 mmol, 0.0033 equiv), dtbpy (1.8 mg, 0.0065 mmol, 0.0065 equiv), B_2pin_2 (231 mg, 0.910 mmol, 0.910 equiv), arene or heteroarene (1.30 mmol, 1.30 equiv), and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), the allylic acetate or chloride (1.00 mmol, 1.00 equiv) and MeOH (3 mL) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 10 min. KF (154 mg, 2.60 mmol, 2.60 equiv) was added and the reaction mixture was sealed and stirred at room temperature for 24 h. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

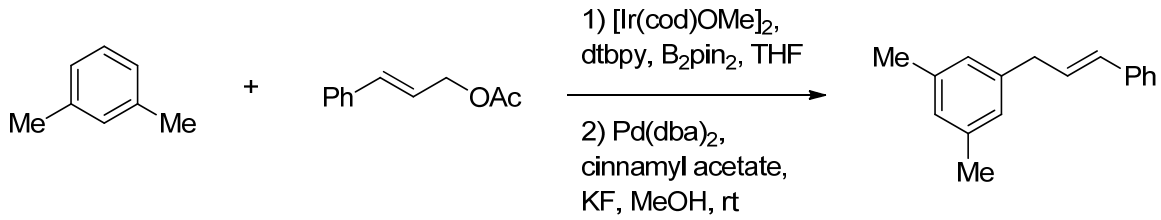


Allylation of 3-chlorotoluene with cinnamyl acetate (1). Prepared according to the general procedure with 3-chlorotoluene (165 mg, 1.30 mmol, 1.30 equiv) and cinnamyl

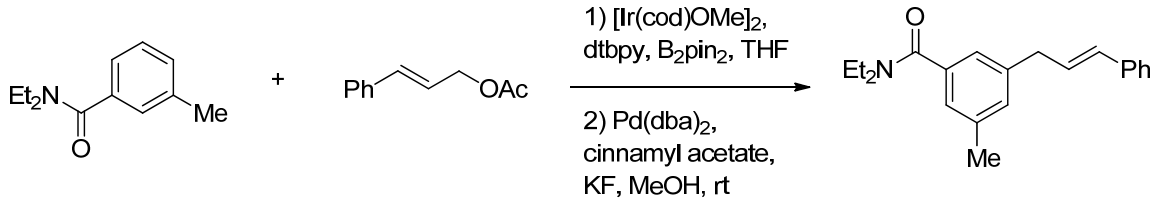
acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (161 mg, 66%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 6.1 Hz, 2H), 6.99 (s, 1H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.37 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.54 (d, *J* = 6.9 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.21, 140.15, 137.55, 134.27, 131.86, 128.82, 128.61, 127.98, 127.55, 127.29, 126.47, 126.06, 39.22, 21.42. HRMS (EI+) calcd for $[C_{16}H_{15}Cl]^+$ m/z = 242.0862, found m/z = 242.0859.



Allylation of methyl *m*-toluate with cinnamyl acetate (2). Prepared according to the general procedure with methyl *m*-toluate (196 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (182 mg, 69%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.40 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28 (s, 1H), 7.24 (m, 3H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.38 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.94 (s, 2H), 3.59 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.56, 140.64, 138.61, 137.52, 134.33, 131.63, 130.50, 128.87, 128.75, 128.37, 127.45, 127.17, 126.39, 52.29, 39.32, 21.46. HRMS (EI+) calcd for $[C_{18}H_{18}O_2]^+$ m/z = 266.1307,found m/z = 266.1313.

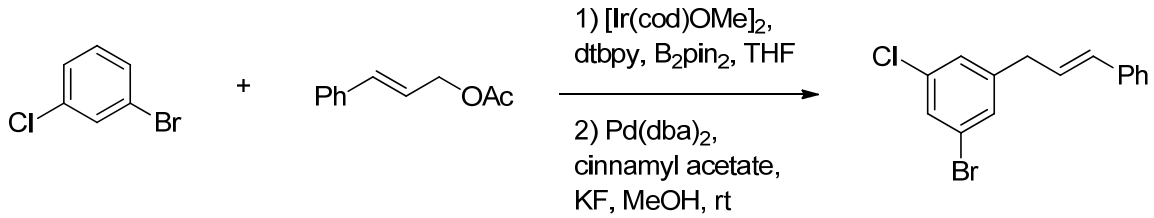


Allylation of *m*-xylene with cinnamyl acetate (3). Prepared according to the general procedure with *m*-xylene (138 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (174 mg, 78%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.25 (m, 1H), 7.14 (m, 1H), 6.91 (s, 2H), 6.51 (dd, *J* = 15.8, 1.4 Hz, 1H), 6.39 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.53 (d, *J* = 6.9 Hz, 2H), 2.35 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.32, 138.27, 131.08, 129.74, 129.00, 128.74, 128.08, 127.30, 126.72, 126.39, 39.53, 21.53. HRMS (EI+) calcd for $[C_{17}H_{18}]^+$ m/z = 222.1409, found m/z = 222.1408.

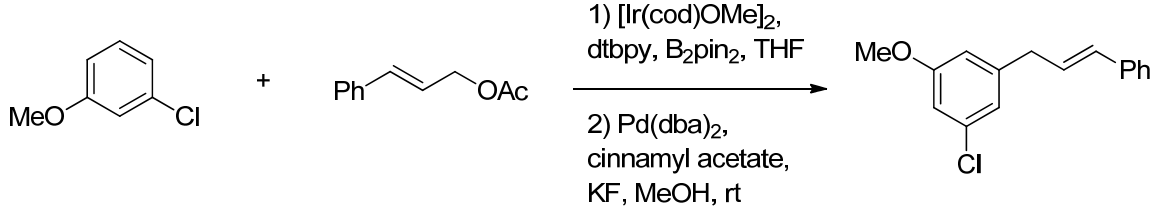


Allylation of *N*,*N*-Diethyl-3-methylbenzamide with cinnamyl acetate (4). Prepared according to the general procedure with *N*,*N*-Diethyl-3-methylbenzamide (249 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (20% EtOAc:80% hexanes) to give the product (237 mg, 77%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.3 Hz, 1H), 7.28 (m, 2H), 7.21 (d, *J* = 2.9 Hz, 1H), 7.19 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 7.04 (s, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.34 (dt, *J* = 15.7, 6.8 Hz, 1H), 3.53 (d, *J* = 6.7 Hz, 2H),

3.25 (s, 4H), 2.37 (s, 3H), 1.18 (d, J = 74.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.77, 140.57, 138.60, 137.69, 137.58, 131.56, 130.38, 128.99, 128.73, 127.39, 126.35, 124.98, 123.73, 43.50, 39.36, 25.00, 21.54, 14.43, 13.14. HRMS (EI+) calcd for $[C_{21}H_{25}NO]^+$ m/z = 307.1936, found m/z = 307.1928.

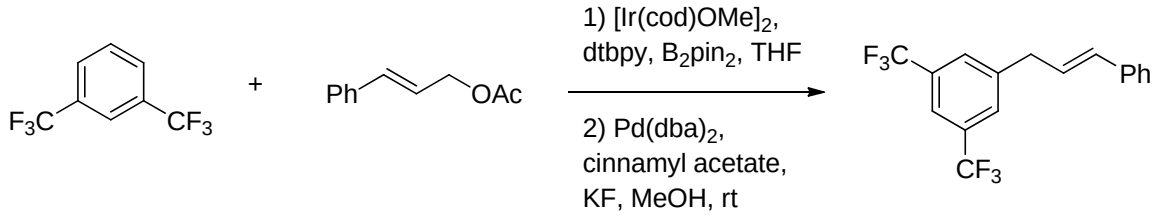


Allylation of 3-bromochlorobenzene with cinnamyl acetate (5). Prepared according to the general procedure with 3-bromochlorobenzene (249 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (175 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.0 Hz, 3H), 7.34 (t, J = 7.6 Hz, 2H), 7.30 (s, 1H), 7.27 (dd, J = 8.4, 6.1 Hz, 1H), 7.19 (s, 1H), 6.49 (d, J = 15.8 Hz, 1H), 6.28 (dt, J = 15.7, 7.0 Hz, 1H), 3.51 (d, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.09, 137.16, 135.29, 132.65, 130.29, 129.49, 128.86, 127.89, 127.79, 127.35, 126.49, 122.98, 38.90. HRMS (EI+) calcd for $[C_{15}H_{12}ClBr]^+$ m/z = 305.9811, found m/z = 305.9827.



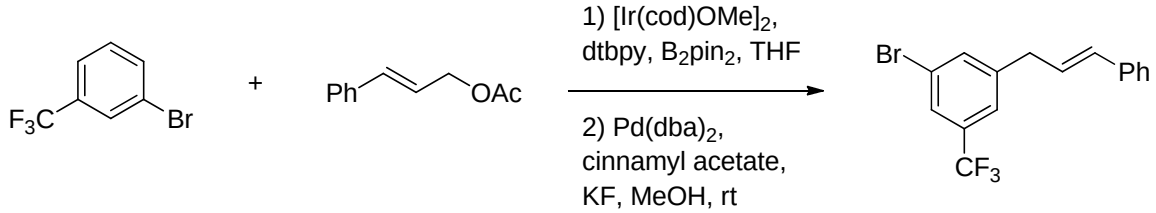
Allylation of 3-chloroanisole with cinnamyl acetate (6). Prepared according to the general procedure with 3-chloroanisole (186 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column

chromatography (5% EtOAc:95% hexanes) to give the product (187 mg, 73%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.32 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.81 (s, 3H), 3.51 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.63, 143.32, 137.44, 135.03, 132.01, 128.79, 128.25, 127.55, 126.43, 121.40, 113.35, 112.19, 55.70, 39.34. HRMS (EI+) calcd for $[C_{16}H_{15}ClO]^+$ m/z = 258.0811, found m/z = 258.0804.



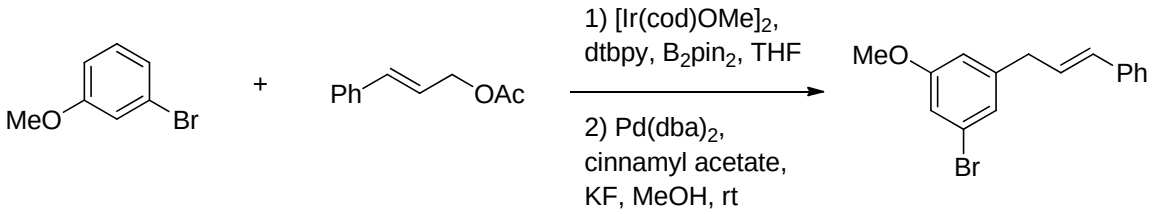
Allylation of 1,3-bis(trifluoromethyl)benzene with cinnamyl acetate (7). Prepared according to the general procedure with 1,3-bis(trifluoromethyl)benzene (279 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (251 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.75 (s, 2H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.36 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.71 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.98, 137.00, 133.14, 131.99 (q, *J* = 33.1 Hz), 129.06 (d, *J* = 3.8 Hz), 128.90, 127.94, 126.83, 126.55, 123.68 (q, *J* = 273 Hz), 120.62 (hept, *J* = 4.0 Hz), 39.15. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.47. HRMS (EI+) calcd for $[C_{17}H_{12}F_6]^+$ m/z = 330.0843, found m/z = 330.0828.

Allylation of 3-methoxybenzotrifluoride with cinnamyl acetate (8). Prepared according to the general procedure with 3-methoxybenzotrifluoride (229 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (247 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 (dd, *J* = 10.3, 4.3 Hz, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 6.99 (s, 1H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.35 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.86 (s, 3H), 3.59 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.18, 143.05, 137.37, 132.19, 132.10 (q, *J* = 32.3 Hz) 128.82, 128.08, 127.63, 126.46, 124.30 (q, *J* = 273 Hz), 118.20 (d, *J* = 1.4 Hz), 117.95 (q, *J* = 3.8 Hz), 108.64 (q, *J* = 3.8 Hz), 55.70, 39.43. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.99. HRMS (EI+) calcd for $[C_{17}H_{15}F_3O]^+$ m/z = 292.1075, found m/z = 292.1057.

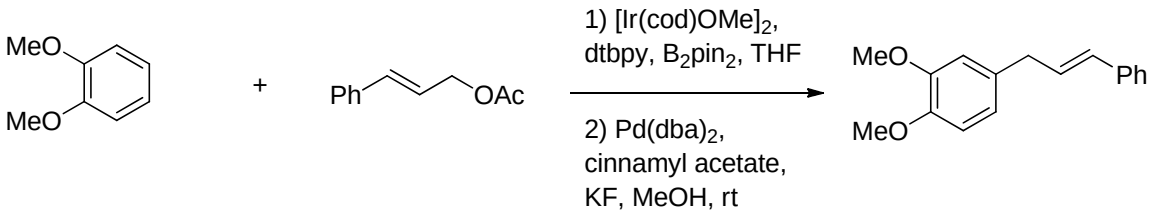


Allylation of 3-bromobenzotrifluoride with cinnamyl acetate (9). Prepared according to the general procedure with 3-bromobenzotrifluoride (293 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (282 mg, 84%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.62 (s, 1H), 7.48 (s, 1H), 7.44 (d, *J* =

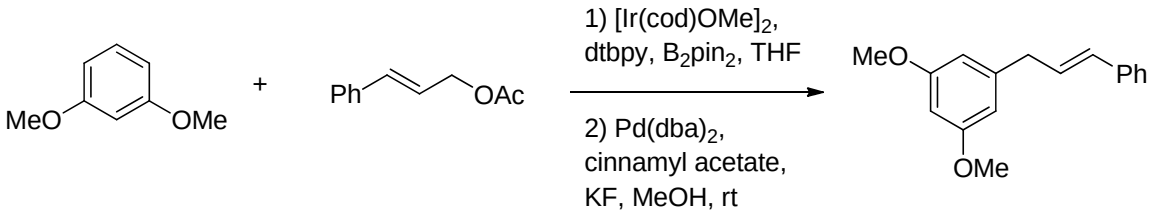
1.4 Hz, 1H), 7.42 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.31 (m, 1H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.33 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.61 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.69, 137.07, 135.31, 132.89, 132.70 (q, *J* = 32.9 Hz), 128.87, 127.85, 127.10, 126.64 (q, *J* = 3.9 Hz), 126.51, 124.43 (q, *J* = 3.7 Hz), 123.45 (q, *J* = 273 Hz), 123.02, 39.01. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.16 . HRMS (EI+) calcd for $[C_{16}H_{12}BrF_3]^+$ m/z = 340.0074, found m/z = 340.0066.



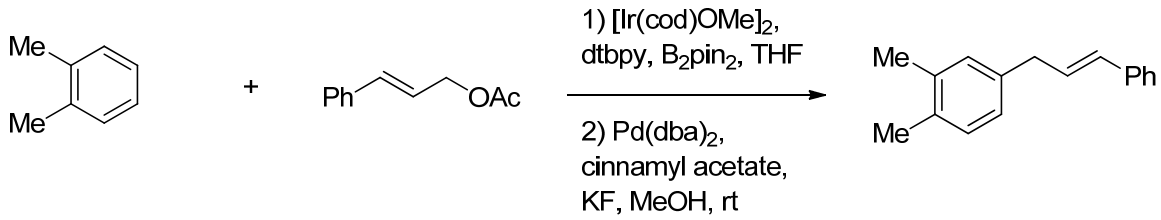
Allylation of 3-bromoanisole with cinnamyl acetate (10). Prepared according to the general procedure with 3-bromoanisole (244 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (230 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.06 (s, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.78 (s, 1H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.35 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.81 (s, 3H), 3.53 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.72, 143.70, 137.47, 132.07, 128.86, 128.28, 127.63, 126.51, 124.37, 123.11, 115.09, 113.96, 55.73, 39.34. HRMS (EI+) calcd for $[C_{16}H_{15}BrO]^+$ m/z = 302.0306, found m/z = 302.0299.



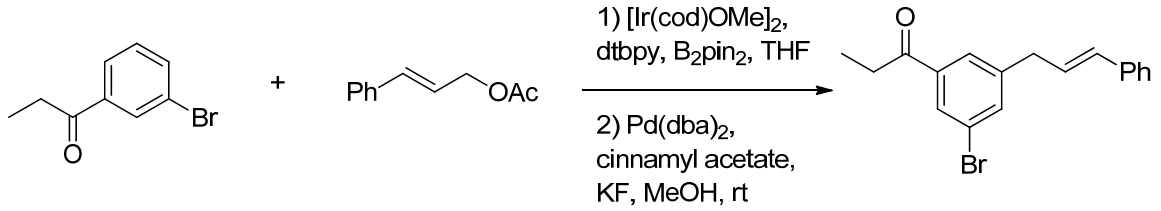
Allylation of veratrole with cinnamyl acetate (11). Prepared according to the general procedure with veratrole (180 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (168 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 2H), 6.82 (m, 3H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.38 (dt, *J* = 15.7, 6.7 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.52 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.18, 147.71, 137.72, 132.95, 131.09, 129.73, 128.77, 127.36, 126.38, 120.76, 112.16, 111.51, 56.19, 56.09, 39.22. HRMS (EI+) calcd for $[C_{17}H_{18}O_2]^+$ m/z = 254.1307, found m/z = 254.1309.



Allylation of 1,3-dimethoxybenzene with cinnamyl acetate (12). Prepared according to the general procedure with 1,3-dimethoxybenzene (180 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (196 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.0, 2H), 7.35 (s, 2H), 7.29 (t, J = 7.6, 2H), 7.20 (m, 1H), 6.46 (d, J = 15.8, 1H), 6.40 (d, J = 2.2, 1H), 6.33 (tt, J = 6.8, 13.6, 1H), 3.77 (s, 6H), 3.48 (d, J = 6.7, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.13, 142.84, 137.67, 131.46, 129.06, 128.73, 127.36, 126.39, 106.92, 98.42, 55.54, 39.85. HRMS (EI+) calcd for $[C_{17}H_{18}O_2]^+$ m/z = 254.1307, found m/z = 254.1304.

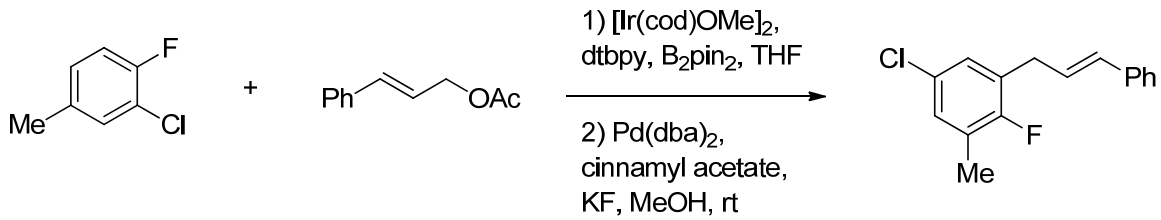


Allylation of *o*-xylene with cinnamyl acetate (13). Prepared according to the general procedure with *o*-xylene (138 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (165 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 10.3, 4.2 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.48 (dt, *J* = 15.7, 6.8 Hz, 1H), 3.61 (d, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.92, 137.90, 136.97, 134.65, 131.08, 130.34, 130.11, 129.98, 128.84, 127.38, 126.48, 126.39, 39.33, 20.13, 19.72. HRMS (EI+) calcd for $[C_{17}H_{18}]^+$ m/z = 222.1408, found m/z = 222.1401.

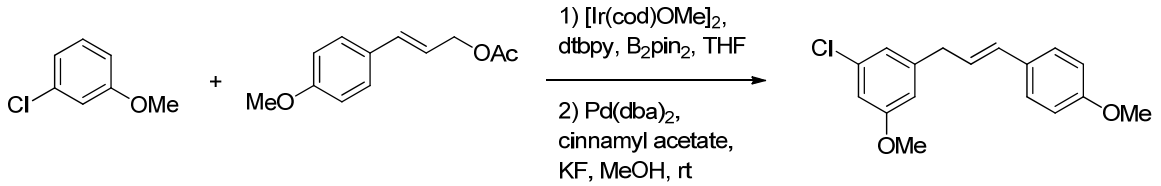


Allylation of 3'-bromopropiophenone with cinnamyl acetate (14). Prepared according to the general procedure with 3'-bromoprophiophenone (277 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (261 mg, 79%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.77 (s, 1H), 7.59 (s, 1H), 7.39 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.31 (dt,

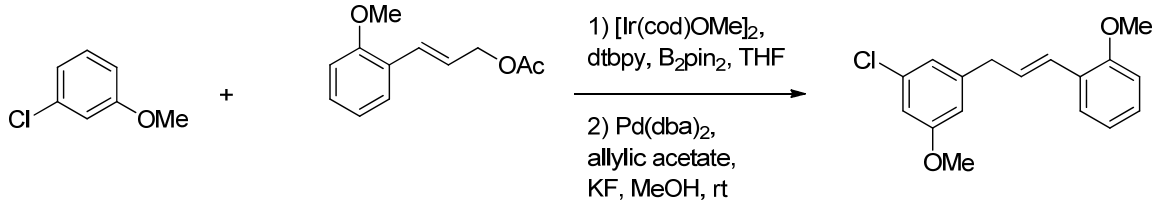
J = 15.7, 6.9 Hz, 1H), 3.59 (d, *J* = 6.8 Hz, 2H), 2.98 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.68, 143.21, 139.05, 137.20, 136.09, 132.53, 129.28, 128.83, 127.73, 127.66, 127.07, 126.47, 123.19, 39.09, 32.23, 8.36. HRMS (EI+) calcd for $[C_{18}H_{17}BrO]^+$ m/z = 328.0462, found m/z = 328.0446.



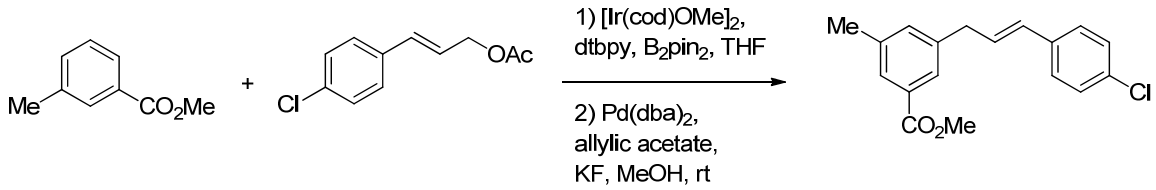
Allylation of 3-chloro-4-fluorotoluene with cinnamyl acetate (15). Prepared according to the general procedure with 3-chloro-4-fluorotoluene (160 mg, 1.30 mmol, 1.30 equiv) and cinnamyl acetate (177 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (187 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.08 (m, 1H), 6.94 (m, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.31 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.55 (d, *J* = 6.9 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.65 (d, *J* = 244.9 Hz), 137.37, 134.47 (d, *J* = 4.4 Hz), 132.04, 129.63 (d, *J* = 3.8 Hz), 129.06, 128.77, 128.47 (d, *J* = 16.0 Hz), 127.57, 127.14, 126.41, 120.60 (d, *J* = 18.4 Hz), 32.70 (d, *J* = 2.8 Hz), 20.80. ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.91. HRMS (EI+) calcd for $[C_{16}H_{14}ClF]^+$ m/z = 260.0768, found m/z = 260.0783.



Allylation of 3-chloroanisole with 4-methoxycinnamyl acetate (46). Prepared according to the general procedure with 3-chloroanisole (186 mg, 1.30 mmol, 1.30 equiv) and 4-methoxycinnamyl acetate (207 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (206 mg, 71%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.89 (s, 1H), 6.87 (s, 2H), 6.79 (s, 1H), 6.71 (s, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.18 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.49 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.63, 159.26, 143.67, 134.99, 131.41, 130.29, 127.57, 126.06, 121.39, 114.22, 113.33, 112.14, 55.69, 55.53, 39.34. HRMS (EI+) calcd for $[C_{17}H_{17}ClO_2]^+$ m/z = 288.0917, found m/z = 288.0910.



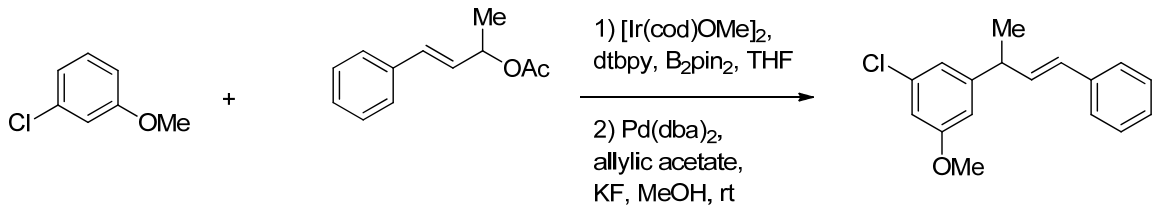
Allylation of 3-chloroanisole with 2-methoxycinnamyl acetate (47). Prepared according to the general procedure with 3-chloroanisole (186 mg, 1.30 mmol, 1.30 equiv) and 2-methoxycinnamyl acetate (207 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (226 mg, 78%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29 (m, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.94 (s, 2H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.84 (m, 1H), 6.78 (d, *J* = 1.2 Hz, 1H), 6.38 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.57 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.68, 156.82, 143.82, 135.01, 128.86, 128.66, 126.99, 126.88, 126.53, 121.44, 120.96, 113.34, 112.20, 111.14, 55.70 (2 carbons), 39.92. HRMS (EI+) calcd for $[C_{17}H_{17}ClO_2]^+$ m/z = 288.0917, found m/z = 288.0911.



Allylation of methyl *m*-toluate with 4-chlorocinnamyl acetate (48). Prepared according to the general procedure with methyl *m*-toluate (195 mg, 1.30 mmol, 1.30 equiv) and 4-chlorocinnamyl acetate (211 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (211 mg, 70%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.27 (m, 5H), 6.41 (m, 1H), 6.32 (dt, J = 15.8, 6.7 Hz, 1H), 3.92 (s, 3H), 3.56 (d, J = 6.7 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.50, 140.36, 138.67, 136.05, 134.29, 133.03, 130.63, 130.44, 129.67, 128.87, 128.46, 127.61, 127.18, 52.27, 39.26, 21.44. HRMS (EI+) calcd for $[C_{18}H_{17}ClO_2]^+$ m/z = 300.0917, found m/z = 344.0925.

Allylation of methyl *m*-toluate with 3-bromocinnamyl acetate (49). Prepared according to the general procedure with methyl *m*-toluate (195 mg, 1.30 mmol, 1.30 equiv) and 3-bromocinnamyl acetate (256 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (269 mg, 78%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.75 (d, J = 9.6 Hz, 2H), 7.52 (t, J = 1.6 Hz, 1H), 7.34 (m, 1H), 7.25 (m, 2H), 7.16 (t, J = 7.8 Hz, 1H), 6.36 (m, 2H), 3.92 (s, 3H), 3.56 (d, J = 5.2 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.46, 140.21, 139.72, 138.70, 134.31, 130.64, 130.62, 130.30, 130.25, 129.28, 128.52, 127.21, 126.43,

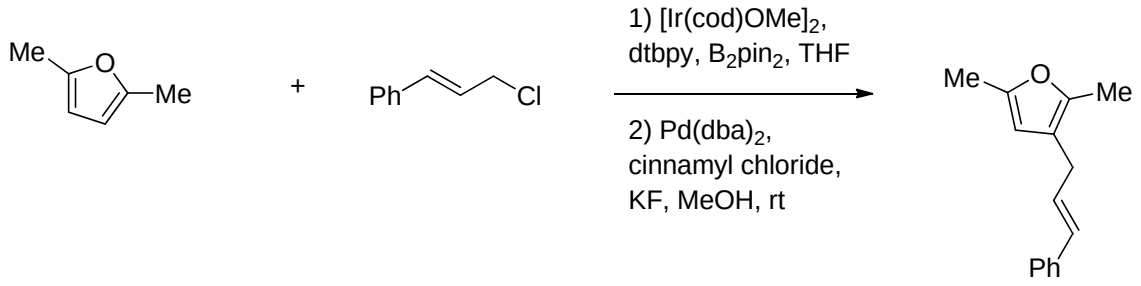
125.09, 122.98, 52.29, 39.25, 21.47. HRMS (EI+) calcd for $[C_{18}H_{17}BrO_2]^+$ m/z = 344.0412, found m/z = 344.0407.



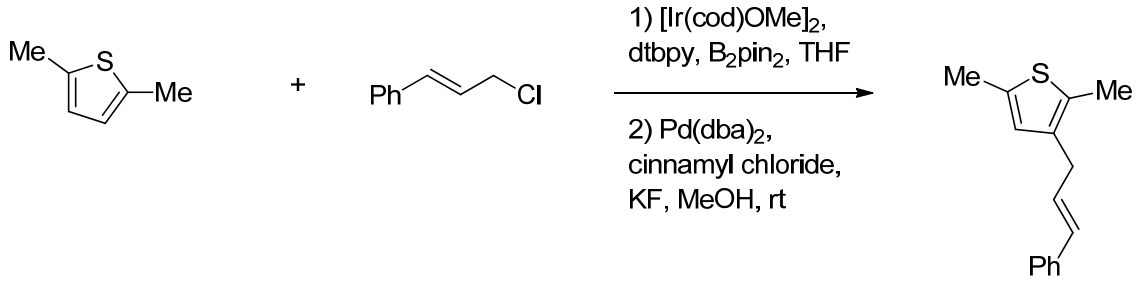
Allylation of 3-chloroanisole with γ-methylcinnamyl acetate (50). Prepared according to the general procedure with 3-chloroanisole (186 mg, 1.30 mmol, 1.30 equiv) and γ-methylcinnamyl acetate (191 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (157 mg, 58%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 (dd, *J* = 11.5, 4.3 Hz, 1H), 6.91 (s, 1H), 6.81 (m, 1H), 6.76 (d, *J* = 1.3 Hz, 1H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.36 (dd, *J* = 15.9, 6.8 Hz, 1H), 3.82 (s, 3H), 3.63 (dd, *J* = 18.2, 11.4 Hz, 1H), 1.49 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.66, 148.90, 137.56, 135.05, 134.36, 129.41, 128.79, 127.51, 126.47, 120.16, 112.33, 112.01, 55.70, 42.76, 21.27. HRMS (EI+) calcd for $[C_{17}H_{17}ClO]^+$ m/z = 292.0968, found m/z = 292.0956.

General Procedure for Allylation of Heteroarenes. Inside a glove box, $[Ir(cod)OMe]_2$ (2.1 mg, 0.0033 mmol, 0.0033 equiv), dtbpy (1.8 mg, 0.0065 mmol, 0.0065 equiv), B_2pin_2 (166 mg, 0.650 mmol, 0.650 equiv), arene or heteroarene (1.30 mmol, 1.30 equiv), and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv) and MeOH (3 mL) were

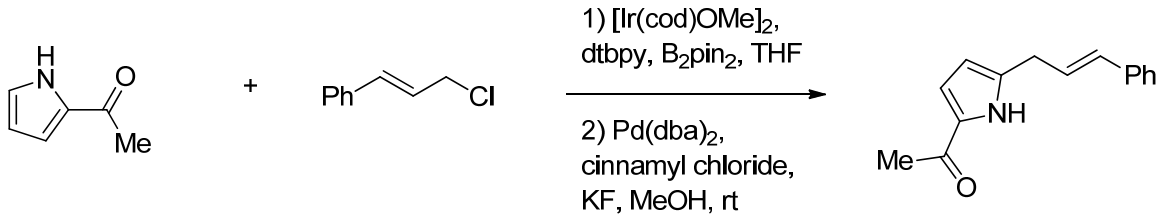
added to the reaction mixture. The reaction mixture was stirred at room temperature for 10 min. KF (154 mg, 2.60 mmol, 2.60 equiv) was added and the reaction mixture was sealed and stirred at room temperature for 24 h. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.



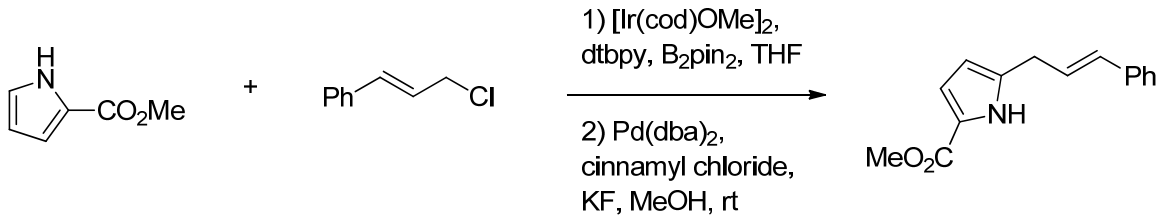
Allylation of 2,5-dimethylfuran with cinnamyl chloride (29). Prepared according to the general procedure with 2,5-dimethylfuran (125 mg, 1.30 mmol, 1.30 equiv) and cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (119 mg, 56%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.38 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 6.30 (dt, J = 15.7, 6.5 Hz, 1H), 5.85 (s, 1H), 3.24 (d, J = 6.4 Hz, 2H), 2.27 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.53, 145.83, 137.84, 130.37, 129.28, 128.72, 127.22, 126.31, 117.48, 108.00, 28.86, 13.72, 11.70. HRMS (EI+) calcd for $[C_{15}H_{16}O]^+$ m/z = 212.1201, found m/z = 212.1210.



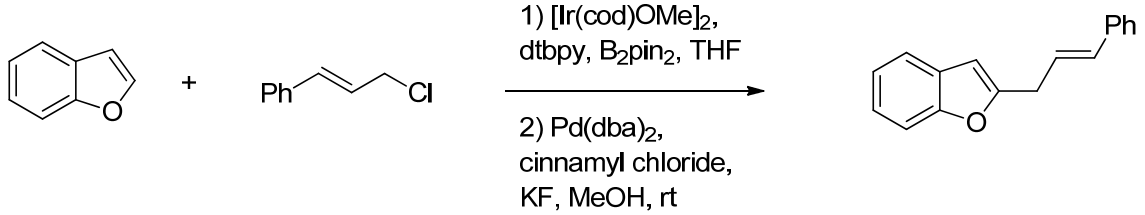
Allylation of 2,5-dimethylthiophene with cinnamyl chloride (30). Prepared according to the general procedure with 2,5-dimethylthiophene (146 mg, 1.30 mmol, 1.30 equiv) and cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (181 mg, 79%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.24 (m, 1H), 6.59 (s, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.37 (dt, *J* = 15.7, 6.5 Hz, 1H), 3.45 (d, *J* = 6.4 Hz, 2H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.86, 135.53, 135.13, 131.25, 130.63, 129.02, 128.79, 127.55, 127.33, 126.40, 32.21, 15.45, 13.17. HRMS (EI+) calcd for $[C_{15}H_{16}S]^+$ m/z = 228.0973, found m/z = 228.0983.



Allylation of 2-acetylpyrrole with cinnamyl chloride (31). Prepared according to the general procedure with 2-acetylpyrrole (142 mg, 1.30 mmol, 1.30 equiv) and cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (119 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.24 (q, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 6.94 (d, *J* = 3.6 Hz, 1H), 6.91 – 6.87 (m, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.35 – 6.25 (m, 2H), 3.60 (d, *J* = 6.8 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.58, 137.25, 132.68, 128.74, 127.65, 126.47, 125.90, 118.33, 117.15, 110.74, 109.29, 31.64, 25.25. HRMS (EI+) calcd for $[C_{15}H_{15}NO_2]^+$ m/z = 225.1154, found m/z = 225.1149.

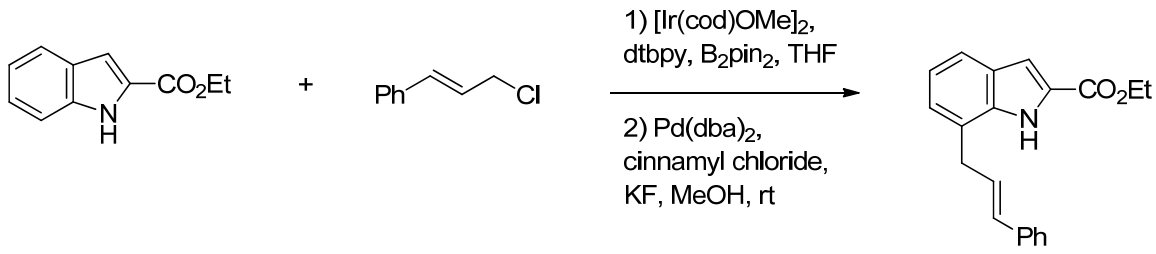


Allylation of methyl pyrrole-2-carboxylate with cinnamyl chloride (32). Prepared according to the general procedure with methyl pyrroles-2-carboxylate (163 mg, 1.30 mmol, 1.30 equiv) and cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (166 mg, 69%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.26 (dd, J = 11.9, 4.4 Hz, 1H), 6.96 (d, J = 17.8 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.52 (d, J = 15.7 Hz, 1H), 6.36 – 6.26 (m, 1H), 6.07 (s, 1H), 3.85 (s, 3H), 3.58 (d, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.83, 137.09, 132.73, 128.82, 127.77, 126.48, 125.94, 121.88, 116.40, 110.70, 109.03, 51.56, 31.73. HRMS (EI+) calcd for $[C_{15}H_{15}NO_2]^+$ m/z = 241.1103, found m/z = 241.1107.



Allylation of benzofuran with cinnamyl chloride (33). Prepared according to the general procedure with benzofuran (154 mg, 1.30 mmol, 1.30 equiv) and cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (122 mg, 52%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.58 – 7.53 (s, 1H), 7.52 – 7.47 (d, J = 7.8 Hz, 2H), 7.46 – 7.41 (s, 2H), 7.40 – 7.33 (s, 2H), 7.31 – 7.21 (m, 2H), 6.67 – 6.59 (d, J = 15.8 Hz, 1H), 6.54 –

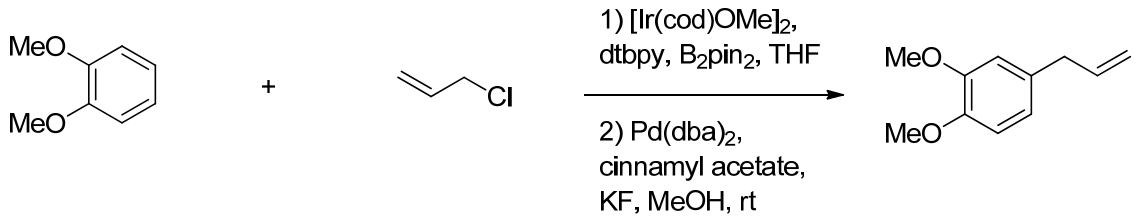
6.50 (s, 1H), 6.48 – 6.38 (dd, J = 14.7, 7.8 Hz, 1H), 3.81 – 3.68 (d, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.37, 155.16, 137.35, 133.00, 129.14, 128.83, 127.72, 126.53, 124.86, 123.66, 122.81, 120.66, 111.14, 103.02, 32.44. HRMS (EI+) calcd for $[C_{17}H_{14}O]^+$ m/z = 234.1045, found m/z = 234.1052.



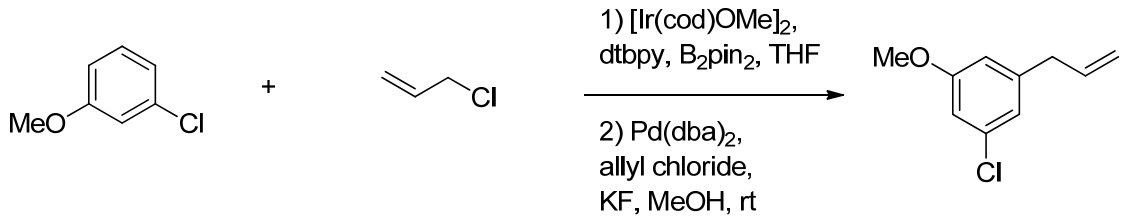
Allylation of ethyl indole-2-carboxylate with cinnamyl chloride (34). Prepared according to the general procedure with ethyl indole-2-carboxylate (246 mg, 1.30 mmol, 1.30 equiv) and cinnamyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (174 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.32 (s, 1H), 7.31 (s, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.20 (m, 2H), 7.18 – 7.11 (m, 1H), 6.59 (d, J = 15.8 Hz, 1H), 6.45 (dt, J = 15.8, 6.6 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.82 (d, J = 6.6 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.42, 137.29, 136.59, 132.07, 128.81, 127.93, 127.75, 127.71, 127.62, 126.45, 125.35, 123.68, 121.37, 121.23, 109.39, 77.60, 77.35, 77.09, 61.33, 35.40, 14.63. HRMS (EI+) calcd for $[C_{20}H_{19}NO_2]^+$ m/z = 305.1416, found m/z = 305.1416.

General Procedure for Allylation of arenes with allyl chloride. Inside a glove box, $[Ir(cod)OMe]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (178 mg, 0.700 mmol, 0.700 equiv), arene (1.30 mmol, 1.30 equiv), and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and

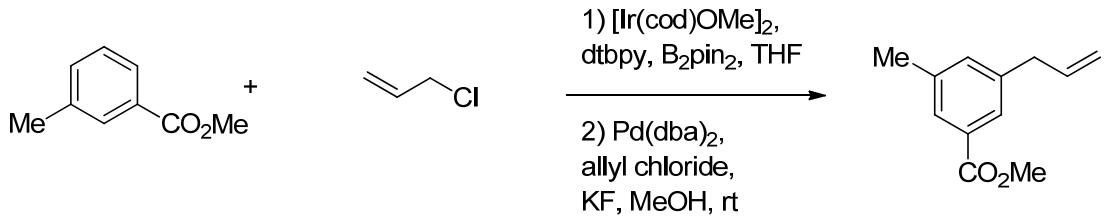
the volatile materials were removed under vacuum. $Pd(dba)_2$ (11.6 mg, 0.02 mmol, 0.02 equiv), allyl chloride (153 mg, 2.00 mmol, 2.00 equiv) and MeOH (3 mL) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 10 min. KF (118 mg, 2.00 mmol, 2.00 equiv) was added and the reaction mixture was sealed and stirred at room temperature for 24 h. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.



Allylation of veratrole with allyl chloride (43). Prepared according to the general procedure with 3-chlorotoluene (138 mg, 1.00 mmol, 1.00 equiv) and allyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (131 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 12.1 Hz, 2H), 5.96 (tt, J = 9.9, 6.7 Hz, 1H), 5.10 (s, 1H), 5.06 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.34 (d, J = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.14, 147.63, 137.91, 132.88, 120.63, 115.81, 112.13, 111.52, 56.18, 56.04, 40.03. HRMS (EI+) calcd for $[C_{11}H_{14}O_2]^+$ m/z = 178.0994, found m/z = 178.0992.

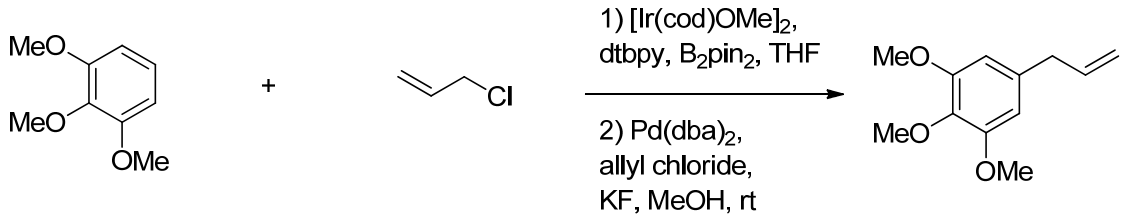


Allylation of 3-chloroanisole with allyl chloride (44). Prepared according to the general procedure with 3-chlorotoluene (142 mg, 1.00 mmol, 1.00 equiv) and allyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (113 mg, 62%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 6.80 (d, J = 1.1 Hz, 1H), 6.76 (s, 1H), 6.64 (d, J = 1.4 Hz, 1H), 5.93 (ddt, J = 16.4, 9.5, 6.7 Hz, 1H), 5.14 (m, 1H), 5.10 (m, 1H), 3.79 (s, 3H), 3.34 (d, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.56, 143.17, 136.60, 134.91, 121.34, 116.80, 113.22, 112.11, 55.64, 40.17. HRMS (EI+) calcd for $[C_{10}H_{11}ClO]^+$ m/z = 182.0499, found m/z = 182.0508.

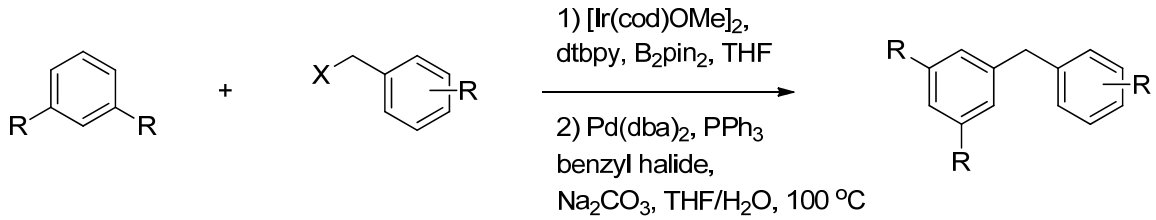


Allylation of methyl *m*-toluate with allyl chloride (45). Prepared according to the general procedure with methyl *m*-toluate (150 mg, 1.00 mmol, 1.00 equiv) and allyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (mg, %). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.69 (s, 1H), 7.20 (s, 1H), 5.96 (ddt, J = 18.9, 9.5, 6.7 Hz, 1H), 5.09 (m, 2H), 3.90 (s, 3H), 3.39 (d, J = 6.7 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.49, 140.49, 138.44, 137.13, 134.24, 130.47, 128.24, 127.11, 116.44,

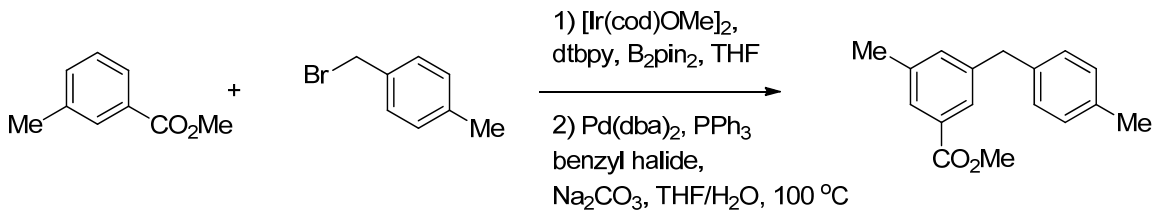
52.17, 40.11, 21.38. HRMS (EI+) calcd for $[C_{12}H_{14}O_2]^+$ m/z = 190.0994, found m/z = 190.1004.



Synthesis of Elemicin (51). Prepared according to the general procedure with 1,2,3-trimethoxybenzene (169 mg, 1.00 mmol, 1.00 equiv) and allyl chloride (153 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (140mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 2H), 5.95 (ddd, *J* = 13.9, 10.1, 4.9 Hz, 1H), 5.10 (t, *J* = 13.7 Hz, 2H), 3.84 (s, 6H), 3.82 (s, 3H), 3.33 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.38, 137.42, 136.02, 123.87, 116.24, 105.57, 61.07, 56.25, 40.77. HRMS (EI+) calcd for $[C_{12}H_{16}O_3]^+$ m/z = 208.1099, found m/z = 208.1092.

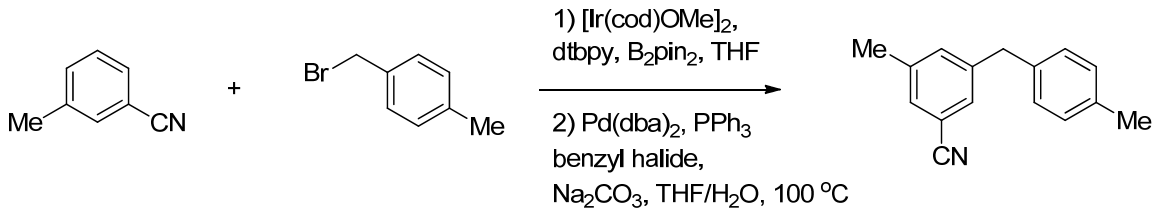


General Procedure for Benzylation of Arenes. Inside a glove box, $[Ir(cod)OMe]_2$ (1.8 mg, 0.0028 mmol, 0.0028 equiv), dtbpy (1.5 mg, 0.0055 mmol, 0.0055 equiv), B_2pin_2 (196 mg, 0.770 mmol, 0.770 equiv), arene (1.10 mmol, 1.10 equiv), and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), PPh_3 (10.5 mg, 0.04 mmol, 0.04 equiv), benzyl halide (1.00 mmol, 1.00 equiv), Na_2CO_3 (424 mg, 4.00 mmol, 4.00 equiv), THF (4 mL) and H_2O (0.4 mL) were added to the reaction mixture. The reaction mixture was sealed and heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

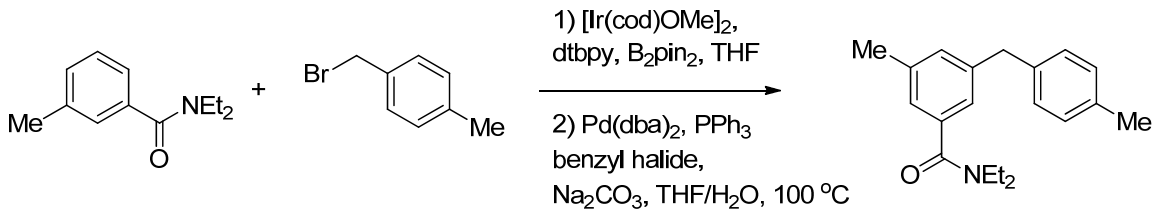


Benzylation of methyl *m*-toluate with 4-Methylbenzyl bromide (16). Prepared according to the general procedure with methyl *m*-toluate (166 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product

(134 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.20 (d, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 5.8 Hz, 4H), 3.95 (s, 2H), 3.90 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.58, 141.88, 138.55, 137.85, 135.96, 134.54, 130.45, 129.48, 128.96, 128.24, 127.42, 126.29, 122.91, 52.25, 41.51, 21.47, 21.26. HRMS (EI+) calcd for $[C_{17}H_{18}O_2]^+$ m/z = 254.1306, found m/z = 254.1301.

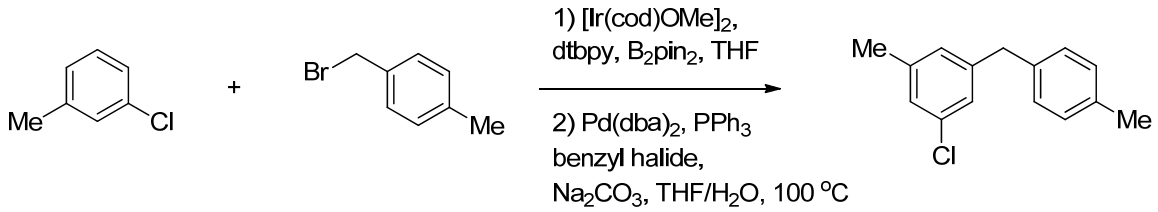


Benzylation of 3-methylbenzonitrile with 4-Methylbenzyl bromide (17). Prepared according to the general procedure with 3-methylbenzonitrile (129 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (182 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 3.92 (s, 2H), 2.35 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.99, 139.54, 136.81, 136.41, 134.50, 130.52, 129.76, 129.66, 129.00, 119.38, 112.48, 41.20, 21.35, 21.28. HRMS (EI+) calcd for $[C_{16}H_{15}N]^+$ m/z = 221.1204, found m/z = 221.1199.

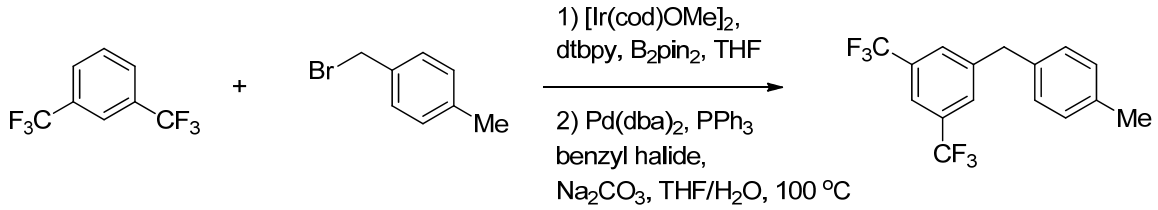


Benzylation of *N,N*-Diethyl-*m*-toluamide with 4-Methylbenzyl bromide (18). Prepared according to the general procedure with *N,N*-Diethyl-*m*-toluamide (211 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv).

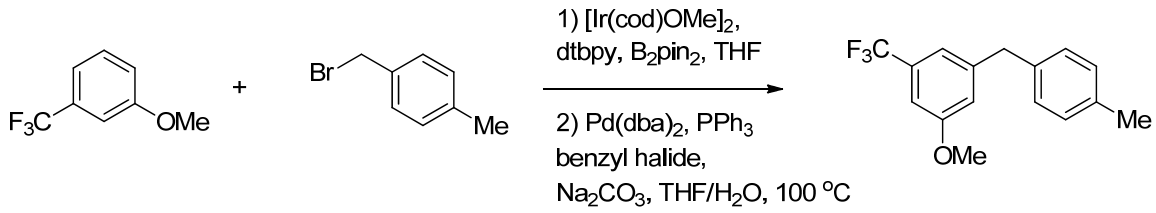
The mixture was purified by flash column chromatography (20% EtOAc:80% hexanes) to give the product (210 mg, 71%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.07 (m, 4H), 7.01 (d, J = 2.1 Hz, 2H), 6.96 (d, J = 1.8 Hz, 1H), 3.90 (s, 2H), 3.41 (m, 4H), 2.31 (s, 3H), 2.31 (s, 3H), 1.13 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.77, 141.75, 138.57, 137.89, 137.56, 135.88, 130.59, 129.40, 129.04, 124.90, 123.95, 43.46, 41.54, 39.34, 21.56, 21.25, 14.36, 13.11. HRMS (EI+) calcd for $[C_{20}H_{25}NO]^+$ m/z = 295.1936, found m/z = 295.1930.



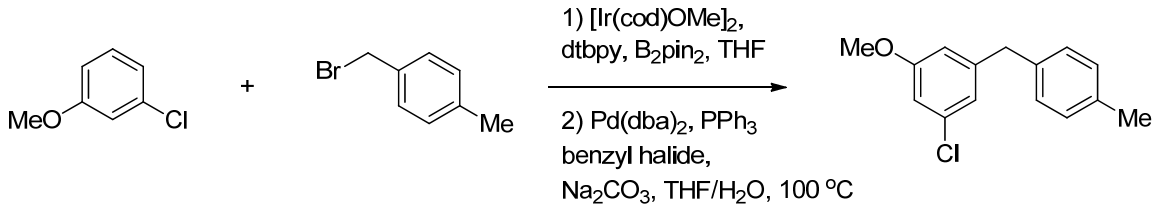
Benzylation of 3-chlorotoluene with 4-Methylbenzyl bromide (19). Prepared according to the general procedure with 3-chlorotoluene (140 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (131 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.03 (s, 1H), 7.01 (s, 1H), 6.91 (s, 1H), 3.90 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.41, 140.05, 137.58, 136.07, 134.15, 129.52, 129.03, 128.17, 127.09, 126.24, 41.40, 21.42, 21.30. HRMS (EI+) calcd for $[C_{15}H_{15}Cl]^+$ m/z = 230.0862, found m/z = 230.0873.



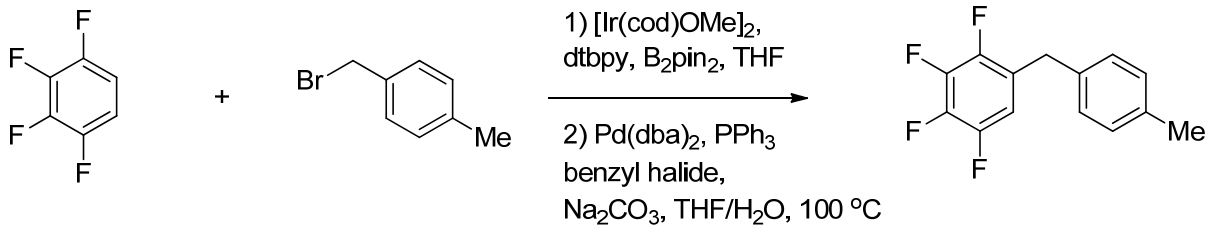
Benzylation of 1,3-bis(trifluoromethyl)benzene with 4-Methylbenzyl bromide (21). Prepared according to the general procedure with 1,3-bis(trifluoromethyl)benzene (236 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (248 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.69 (s, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.10 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.17, 136.79, 136.00, 131.93 (q, *J* = 33.1 Hz), 129.85, 129.17 (d, *J* = 3.8 Hz), 129.00, 123.65 (q, *J* = 273 Hz), 120.44 (hept, *J* = 4.1 Hz), 41.35, 21.21. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.33. HRMS (EI+) calcd for $[C_{16}H_{12}F_6]^+$ m/z = 318.0843, found m/z = 318.0853.



Benzylation of 3-methoxybenzotrifluoride with 4-Methylbenzyl bromide (22). Prepared according to the general procedure with 3-methoxybenzotrifluoride (193 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (197 mg, 69%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.9 Hz, 2H), 7.08 (m, 3H), 6.98 (s, 1H), 6.90 (s, 1H), 3.97 (s, 2H), 3.82 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.10, 144.18, 137.04, 136.24, 132.01 (q, *J* = 32 Hz), 129.56, 128.97, 124.25 (q, *J* = 273 Hz), 118.51, 118.18 (q, *J* = 3.9 Hz), 108.38 (q, *J* = 3.9 Hz), 55.66, 41.61, 21.23. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.02. HRMS (EI+) calcd for $[C_{16}H_{15}F_3O]^+$ m/z = 280.1075, found m/z = 280.1062.

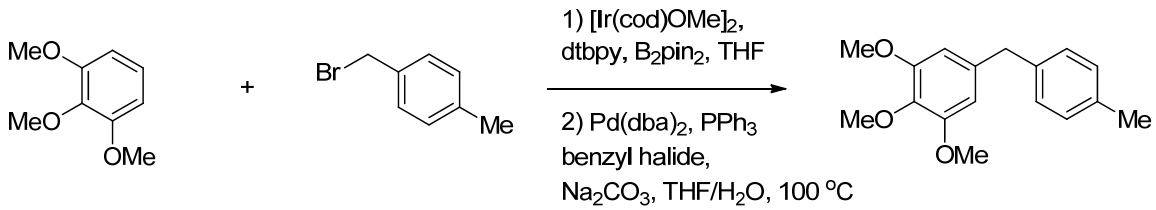


Benzylation of 3-chloroanisole with 4-Methylbenzyl bromide (23). Prepared according to the general procedure with 3-chloroanisole (157 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (197 mg, 80%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.11 (m, 4H), 6.79 (s, 1H), 6.75 (s, 1H), 6.64 (s, 1H), 3.88 (s, 2H), 3.77 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.57, 144.53, 137.23, 136.14, 134.97, 129.51, 129.01, 121.64, 113.69, 111.95, 55.64, 41.55, 21.26. HRMS (EI+) calcd for $[C_{15}H_{15}ClO]^+$ m/z = 246.0812, found m/z = 246.0817.

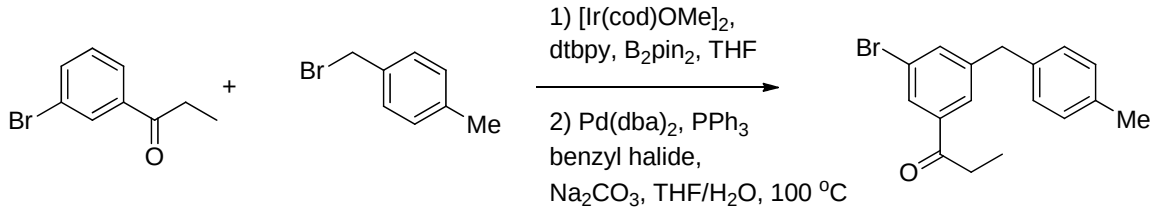


Benzylation of 1,2,3,4-tetrafluorobenzene with 4-Methylbenzyl bromide (24). Prepared according to the general procedure with 1,2,3,4-tetrafluorobenzene (166 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (226 mg, 89%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.22 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 7.4 Hz, 2H), 6.79 (d, J = 8.0 Hz, 1H), 4.00 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.51 (m), 145.67 (m), 141.35 (m), 139.08 (m), 136.83, 135.12,

129.78, 128.92, 125.26 (ddd, J = 14.8, 6.5, 4.1 Hz), 111.70 (dt, J = 19.5, 3.8 Hz), 33.95, 21.14. ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.43 (dt, J = 22.1, 11.6 Hz), -143.89 (m), -156.65 (t, J = 20.0 Hz), -159.46 (td, J = 20.4, 8.1 Hz). HRMS (EI+) calcd for $[C_{14}H_{10}F_4]^+$ m/z = 254.0719, found m/z = 254.0727.

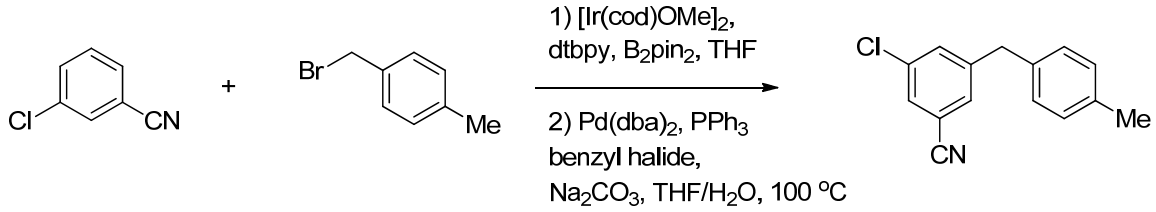


Benzylation of 1,2,3-trimethoxybenzene with 4-Methylbenzyl bromide (25). Prepared according to the general procedure with 1,2,3-trimethoxybenzene (186 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (193 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.41 (s, 2H), 3.89 (s, 2H), 3.83 (s, 3H), 3.82 (s, 6H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.39, 138.07, 137.27, 136.44, 135.89, 129.40, 128.88, 106.06, 61.09, 56.27, 42.06, 21.27. HRMS (EI+) calcd for $[C_{17}H_{20}O_3]^+$ m/z = 272.1412, found m/z = 272.1405.

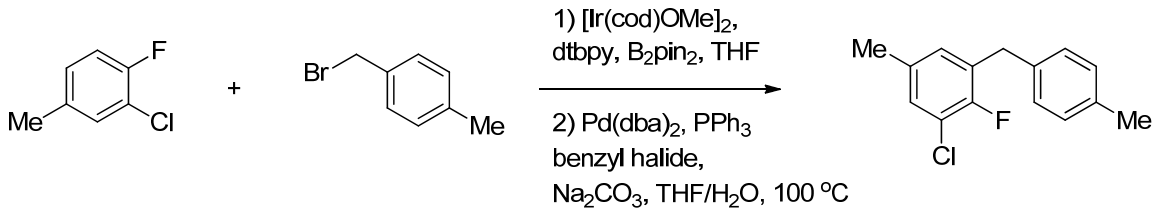


Benzylation of 3'-bromopropiophenone with 4-Methylbenzyl bromide (26). Prepared according to the general procedure with 3'-bromopropiophenone (235 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the

product (159 mg, 50%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.73 (s, 1H), 7.51 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 3.97 (s, 2H), 2.95 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.68, 144.44, 138.96, 136.72, 136.43, 136.24, 129.68, 129.12, 128.98, 127.23, 123.15, 41.31, 32.20, 21.26, 8.33. HRMS (EI+) calcd for $[C_{17}H_{17}BrO]^+$ m/z = 316.0463, found m/z = 316.0456.

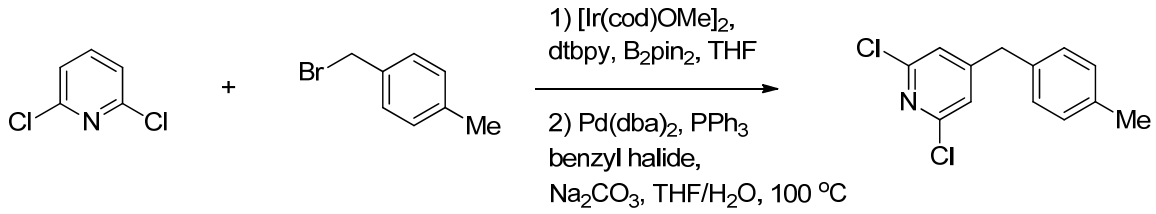


Benzylation of 3-chlorobenzonitrile with 4-Methylbenzyl bromide (27). Prepared according to the general procedure with 3-chlorobenzonitrile (152 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (195 mg, 81%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.42 (s, 1H), 7.36 (s, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 3.96 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.24, 136.87, 135.70, 135.40, 133.78, 130.82, 129.87, 129.77, 129.05, 117.81, 114.09, 41.00, 21.28. HRMS (EI+) calcd for $[C_{15}H_{12}ClN]^+$ m/z = 241.0658, found m/z = 241.0656.



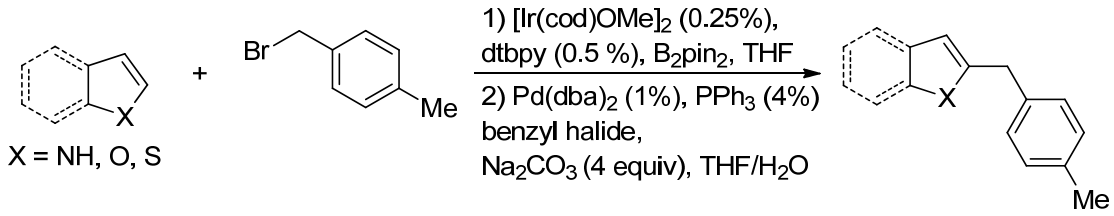
Benzylation of 3-chloro-4-fluorotoluene with 4-Methylbenzyl bromide (28). Prepared according to the general procedure with 3-chloro-4-fluorotoluene (160 mg, 1.10 mmol,

1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (205 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 4H), 7.08 (d, J = 6.5 Hz, 1H), 6.87 (d, J = 6.3 Hz, 1H), 3.96 (s, 2H), 2.37 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.67 (d, J = 244.8 Hz), 136.53, 136.22, 134.44 (d, J = 4.5 Hz), 129.97 (d, J = 3.7 Hz), 129.78 (d, J = 15.8 Hz), 129.55, 129.01, 128.92, 120.64 (d, J = 18.4 Hz), 34.87 (d, J = 2.5 Hz), 21.30, 20.82. ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.66. HRMS (EI+) calcd for $[C_{15}H_{14}ClF]^+$ m/z = 248.0768, found m/z = 248.0775.

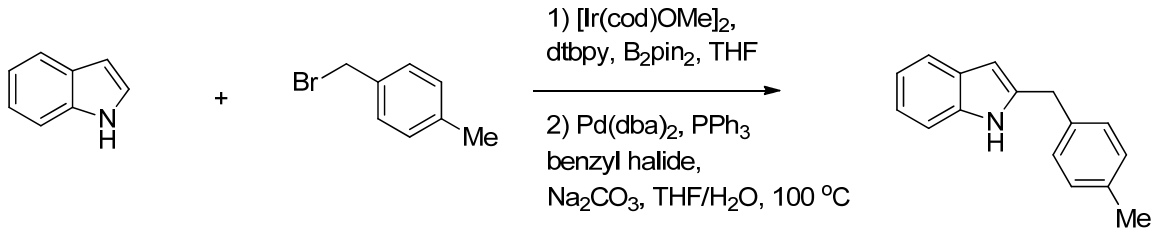


Benzylation of 2,6-dichloropyridine with 4-Methylbenzyl bromide (42). Inside a glove box, $[Ir(cod)OMe]_2$ (21.6 mg, 0.033 mmol, 0.033 equiv), dtbpy (18 mg, 0.066 mmol, 0.066 equiv), B_2pin_2 (196 mg, 0.770 mmol, 0.770 equiv), 2,6-dichloropyridine (163 mg, 1.10 mmol, 1.10 equiv) and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), PPh_3 (10.5 mg, 0.04 mmol, 0.04 equiv), 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv), Na_2CO_3 (424 mg, 4.00 mmol, 4.00 equiv), THF (4 mL) and H_2O (0.4 mL) were added to the reaction mixture. The reaction mixture was sealed and heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The mixture was purified by flash column chromatography

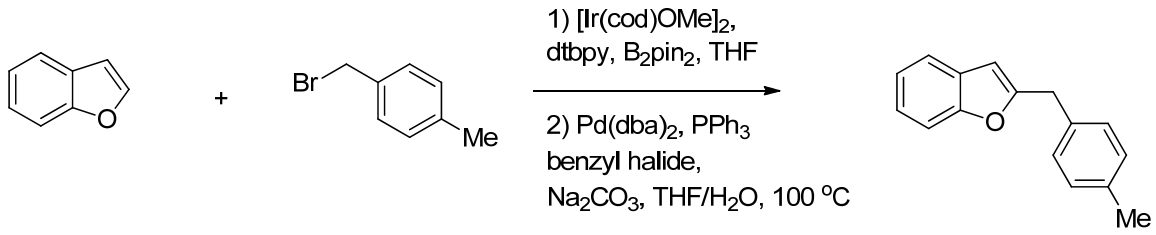
(10% EtOAc:90% hexanes) to give the product (177 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, J = 7.7 Hz, 2H), 7.06 (d, J = 2.8 Hz, 2H), 7.04 (s, 2H), 3.90 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.66, 150.77, 137.17, 134.36, 129.95, 129.14, 123.33, 40.55, 21.31. HRMS (EI+) calcd for $[C_{13}H_{11}Cl_2N]^+$ m/z = 251.0268, found m/z = 251.0263. Anal Calc. for $C_{13}H_{11}NCl_2$: C, 61.93; H, 4.40; N, 5.56. Found: C, 62.05; H, 4.29; N, 5.39.



General Procedure for Benzylation of Heteroarenes. Inside a glove box, $[Ir(cod)OMe]_2$ (1.8 mg, 0.0028 mmol, 0.0028 equiv), dtbpy (1.5 mg, 0.0055 mmol, 0.0055 equiv), B_2pin_2 (140 mg, 0.550 mmol, 0.550 equiv), heteroarene (1.10 mmol, 1.10 equiv), and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), PPh_3 (10.5 mg, 0.04 mmol, 0.04 equiv), benzyl halide (1.00 mmol, 1.00 equiv), Na_2CO_3 (424 mg, 4.00 mmol, 4.00 equiv), THF (4 mL) and H_2O (0.4 mL) were added to the reaction mixture. The reaction mixture was sealed and heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

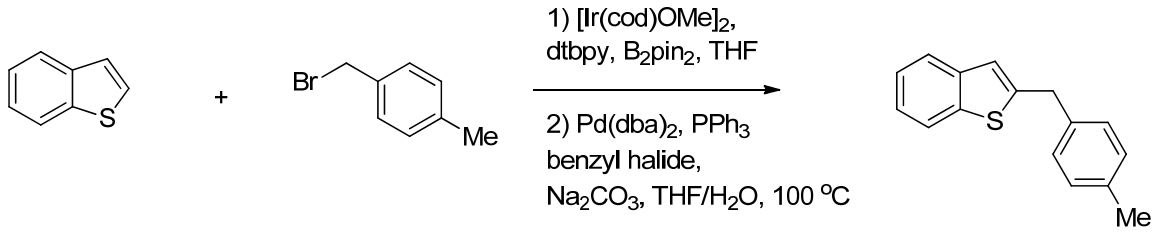


Benzylation of Indole with 4-Methylbenzyl bromide (35). Prepared according to the general procedure with indole (129 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (128 mg, 58%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.68 – 7.59 (m, 1H), 7.37 – 7.07 (m, 7H), 6.45 – 6.35 (m, 1H), 4.14 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.44, 136.61, 136.56, 135.76, 129.71, 129.06, 128.53, 121.54, 120.28, 120.00, 110.80, 101.24, 34.56, 21.37. HRMS (EI+) calcd for $[C_{16}H_{15}N]^+$ m/z = 221.1204, found m/z = 221.1199. Anal Calc. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.51; H, 6.69; N, 5.99.

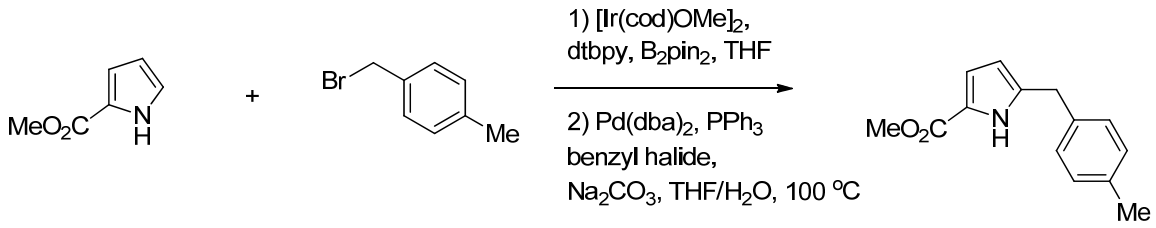


Benzylation of benzofuran with 4-Methylbenzyl bromide (36). Prepared according to the general procedure with benzofuran (130 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (154 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.37 – 7.30 (m, 5H), 7.28 (s, 1H), 7.27 (s, 1H), 6.49 (d, J = 0.6 Hz, 1H), 4.19 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.50, 155.36, 136.66, 134.53, 129.68, 129.24,

129.19, 123.73, 122.87, 120.76, 111.29, 103.60, 34.95, 21.45. HRMS (EI+) calcd for $[C_{16}H_{14}O]^+$ m/z = 222.1044, found m/z = 222.1040.

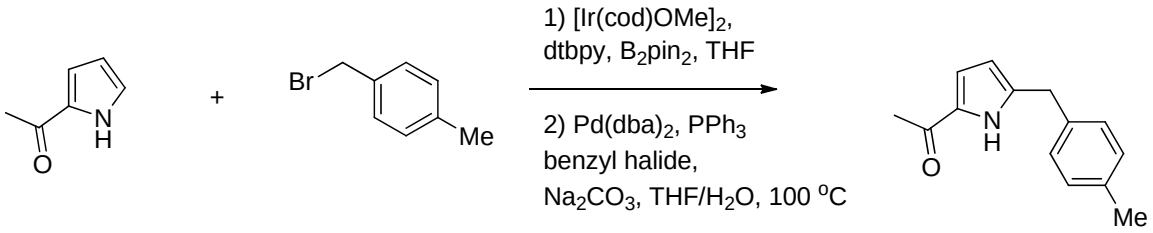


Benzylation of benzothiophene with 4-Methylbenzyl bromide (37). Prepared according to the general procedure with benzothiophene (148 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (198 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.10 (s, 1H), 4.29 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.93, 140.45, 140.20, 136.88, 136.62, 129.67, 129.03, 124.46, 123.95, 123.28, 122.52, 121.84, 36.94, 21.47. HRMS (EI+) calcd for $[C_{16}H_{14}S]^+$ m/z = 238.0816, found m/z = 238.0818. Anal Calc. for $C_{16}H_{14}S$: C, 80.63; H, 5.92. Found: C, 80.33; H, 5.95.

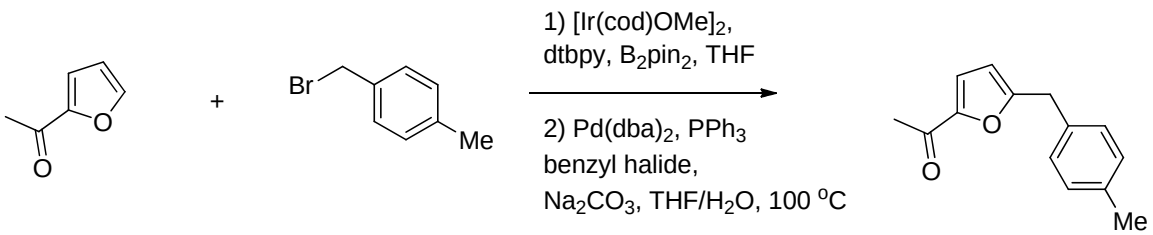


Benzylation of Methyl Pyrrole-2-carboxylate with 4-Methylbenzyl bromide (38). Prepared according to the general procedure with methyl pyrrole-2-carboxylate (138 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes)

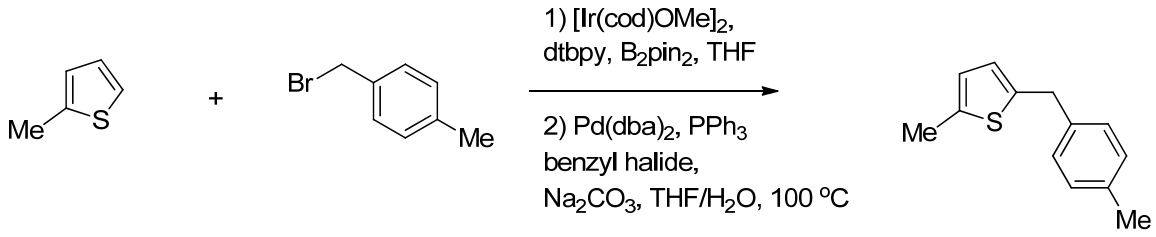
to give the product (173 mg, 76%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.92 – 6.78 (m, 1H), 6.10 – 5.97 (m, 1H), 3.96 (s, 2H), 3.81 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.77, 137.28, 136.62, 135.23, 129.70, 128.79, 121.84, 116.25, 109.32, 51.49, 33.99, 21.24. HRMS (EI+) calcd for $[C_{14}H_{15}NO_2]^+$ m/z = 229.1103, found m/z = 229.1110. Anal Calc. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.14; H, 6.75; N, 6.07.



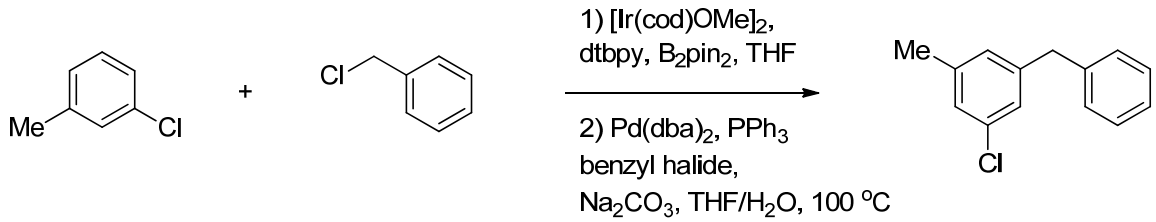
Benzylation of 2-Acetylpyrrole with 4-Methylbenzyl bromide (39). Prepared according to the general procedure with 2-acetylpyrrole (120 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (104 mg, 49%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.84 (dd, *J* = 3.6, 2.6 Hz, 1H), 6.11 – 5.97 (m, 1H), 3.96 (s, 2H), 2.38 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.42, 139.50, 136.66, 134.99, 131.76, 129.71, 128.83, 117.97, 109.56, 34.01, 25.26, 21.25. HRMS (EI+) calcd for $[C_{14}H_{15}NO]^+$ m/z = 213.1154, found m/z =213.1164. Anal Calc. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.44; H, 7.07; N, 6.58.



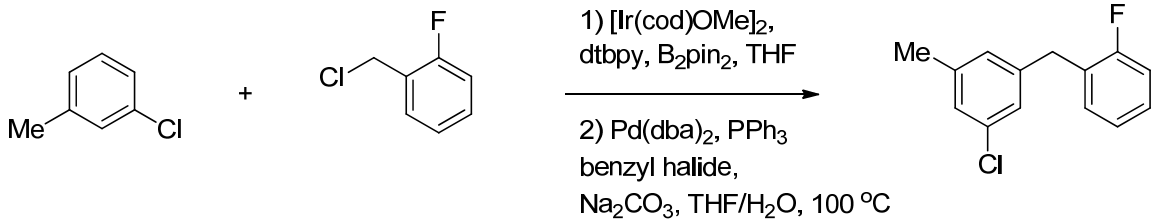
Benzylation of 2-acetylfuran with 4-Methylbenzyl bromide (40). Prepared according to the general procedure with 2-acetylfuran (121 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (146 mg, %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 4H), 7.09 (d, *J* = 3.5 Hz, 1H), 6.09 (d, *J* = 3.5 Hz, 1H), 4.00 (s, 2H), 2.42 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.54, 160.74, 152.06, 136.78, 133.64, 129.62, 128.96, 119.29, 109.43, 34.67, 26.01, 21.28. HRMS (EI+) calcd for $[C_{14}H_{14}O_2]^+$ m/z = , found m/z = .



Benzylation of 2-methylthiophene with 4-Methylbenzyl bromide (41). Prepared according to the general procedure with 2-methylthiophene (108 mg, 1.10 mmol, 1.10 equiv) and 4-Methylbenzyl bromide (186 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (131 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 3.3 Hz, 1H), 6.66 (dd, *J* = 3.3, 1.0 Hz, 1H), 4.14 (s, 2H), 2.52 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.55, 138.61, 137.93, 136.21, 129.54, 128.78, 125.03, 125.00, 36.23, 21.42, 15.67. HRMS (EI+) calcd for $[C_{13}H_{14}S]^+$ m/z = 202.0816, found m/z = 202.0811.

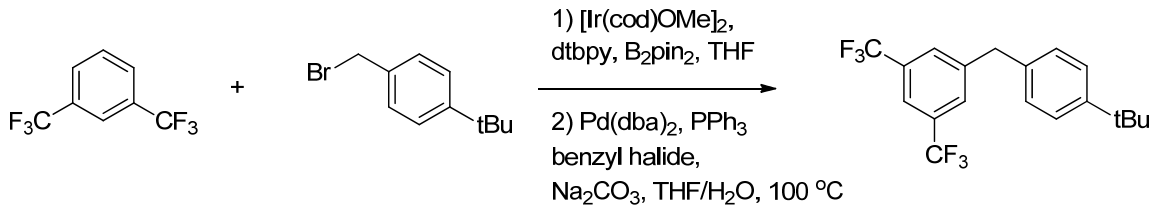


Benzylation of 3-chlorotoluene with benzyl chloride (52). Prepared according to the general procedure with 3-chlorotoluene (140 mg, 1.10 mmol, 1.10 equiv) and benzyl chloride (127 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (160 mg, 74%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.09 (s, 1H), 7.07 (s, 1H), 6.96 (s, 1H), 3.98 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.15, 140.66, 140.13, 134.26, 129.21, 128.88, 128.28, 127.23, 126.61, 126.36, 41.86, 21.45. HRMS (EI+) calcd for $[C_{14}H_{13}Cl]^+$ m/z = 216.0706, found m/z = 216.0704.

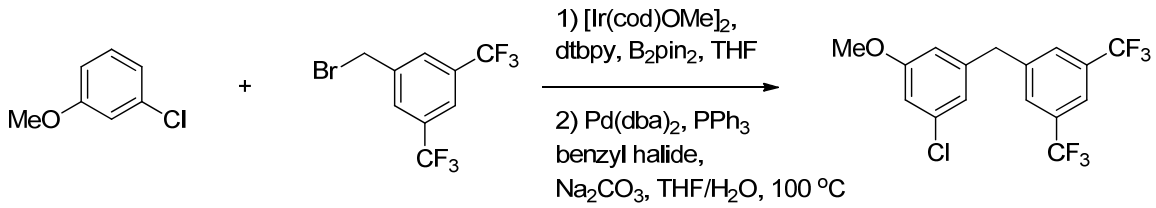


Benzylation of 3-chlorotoluene with 2-fluorobenzyl chloride (53). Prepared according to the general procedure with 3-chlorotoluene (140 mg, 1.10 mmol, 1.10 equiv) and 2-fluorobenzyl chloride (145 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (185 mg, 79%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 13.9, 6.8 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.10 (d, *J* = 1.1 Hz, 1H), 7.08 (d, *J* = 6.9 Hz, 2H), 6.97 (s, 1H), 3.98 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.14 (d, *J* = 246 Hz), 160.61 ,

142.98 , 135.04 , 131.26 (d, J = 4.5 Hz), 128.57 (d, J = 8.1 Hz), 127.30 (d, J = 15.9 Hz), 124.46 (d, J = 3.5 Hz), 121.50 , 115.69 (d, J = 21.9 Hz), 113.63 , 112.18 , 55.64 , 34.87 (d, J = 3.1 Hz). HRMS (EI+) calcd for $[C_{14}H_{12}ClF]^+$ m/z = 234.0612, found m/z = 234.0617.

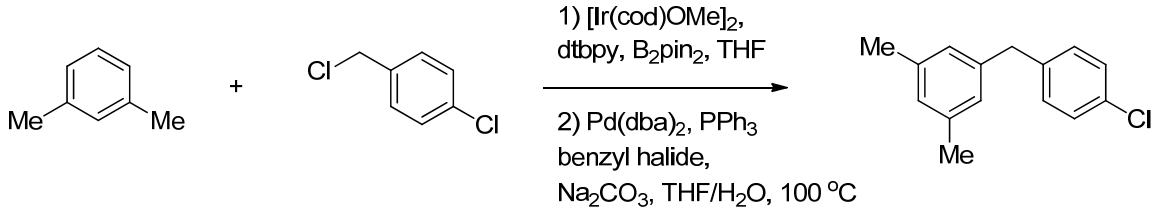


Benzylation of 1,3-bis(trifluoromethyl)benzene with 4-*tert*-butylbenzyl bromide (54). Prepared according to the general procedure with 1,3-bis(trifluoromethyl)benzene (236 mg, 1.10 mmol, 1.10 equiv) and 4-*tert*-butylbenzyl bromide (228 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (293 mg, 81%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (s, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.11 (s, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.07, 143.96, 136.00, 131.93 (q, J = 33.1 Hz), 129.26 (d, J = 4.1 Hz), 128.69, 126.07, 123.64 (q, J = 273 Hz), 120.47 (p, J = 4.9, 4.4 Hz), 41.29, 34.70, 31.55. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.28. HRMS (EI+) calcd for $[C_{19}H_{18}F_6]^+$ m/z = 360.1313, found m/z = 360.1321.

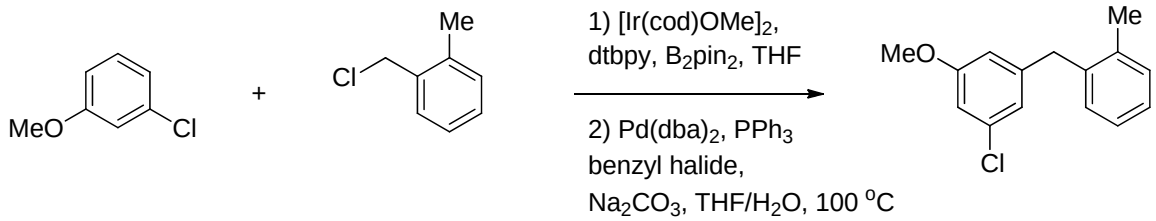


Benzylation of 3-chloroanisole with 3,5-(bistrifluoromethyl)benzyl bromide (55). Prepared according to the general procedure with 3-chloroanisole (157 mg, 1.10 mmol, 1.10 equiv) and 3,5-(bistrifluoromethyl)benzyl bromide (307 mg, 1.00 mmol, 1.00 equiv).

The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (328 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.62 (s, 2H), 6.80 (t, *J* = 2.0 Hz, 1H), 6.76 (s, 1H), 6.58 (s, 1H), 4.02 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.86, 142.74, 141.73, 135.57, 132.10 (q, *J* = 33.2 Hz), 129.19 (d, *J* = 3.9 Hz), 123.51 (q, *J* = 273 Hz), 121.55, 120.85 (m), 113.92, 112.64, 55.71, 41.39. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.34. HRMS (EI+) calcd for $[C_{16}H_{11}ClF_6O]^+$ m/z = 368.0404, found m/z = 368.0415.

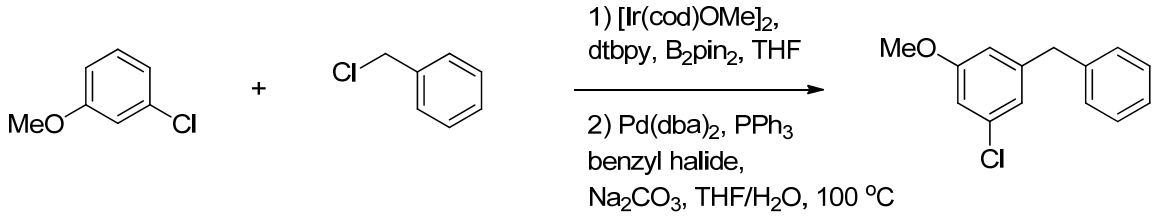


Benzylation of *m*-xylene with 4-chlorobenzyl chloride (56). Prepared according to the general procedure with *m*-xylene (117 mg, 1.10 mmol, 1.10 equiv) and 4-chlorobenzyl chloride (162 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (129 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.91 (s, 1H), 6.84 (s, 2H), 3.91 (s, 2H), 2.33 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.71, 140.10, 138.34, 132.03, 130.51, 128.79, 128.21, 126.97, 41.40, 21.56. HRMS (EI+) calcd for $[C_{15}H_{15}Cl]^+$ m/z = 230.0862, found m/z = 230.0865.

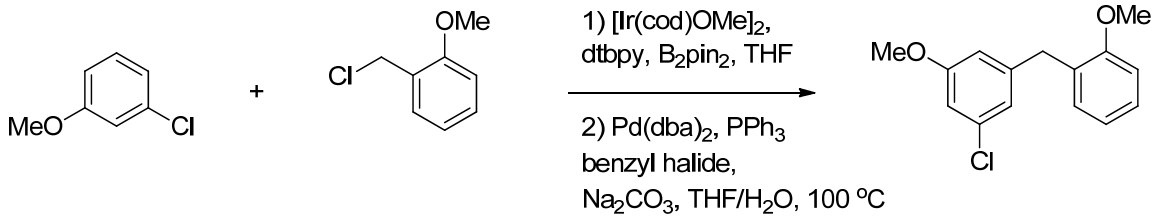


Benzylation of 3-chloroanisole with 2-methylbenzyl chloride (57). Prepared according to the general procedure with 3-chloroanisole (157 mg, 1.10 mmol, 1.10 equiv) and 2-

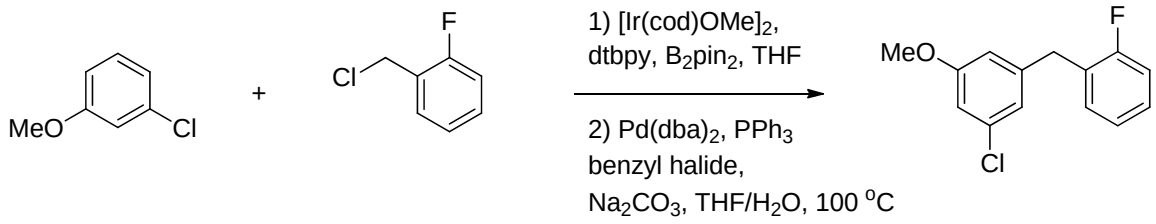
methylbenzyl chloride (141 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (228 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 6.1, 3.5 Hz, 3H), 7.15 (d, *J* = 5.2 Hz, 1H), 6.78 (m, 2H), 6.62 (s, 1H), 3.97 (s, 2H), 3.78 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.59, 143.72, 138.11, 136.87, 135.03, 130.70, 130.24, 127.07, 126.42, 121.51, 113.66, 111.83, 55.64, 39.52, 19.95. HRMS (EI+) calcd for $[C_{15}H_{15}ClO]^+$ m/z = 246.0812, found m/z = 246.0818.



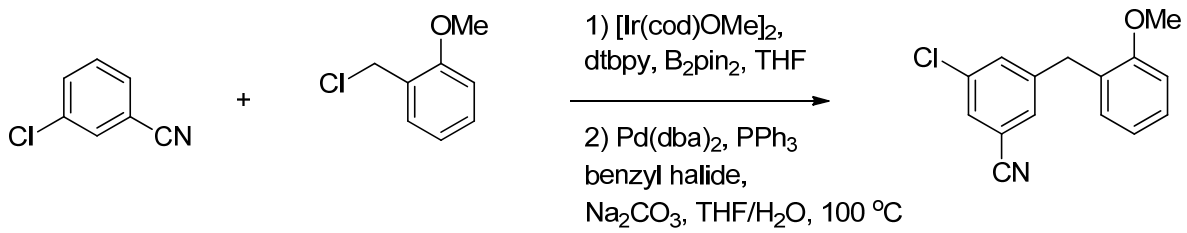
Benzylation of 3-chloroanisole with benzyl chloride (58). Prepared according to the general procedure with 3-chloroanisole (157 mg, 1.10 mmol, 1.10 equiv) and benzyl chloride (127 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (195 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.81 (s, 1H), 6.77 (s, 1H), 6.65 (s, 1H), 3.93 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.56, 144.21, 140.29, 135.00, 129.15, 128.85, 126.64, 121.69, 113.76, 111.98, 55.66, 41.95. HRMS (EI+) calcd for $[C_{14}H_{13}ClO]^+$ m/z = 232.0655, found m/z = 232.0665.



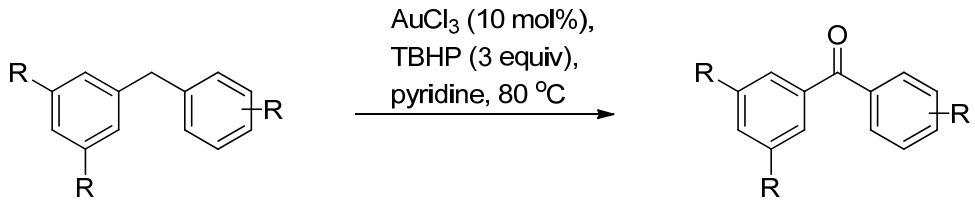
Benzylation of 3-chloroanisole with 2-methoxybenzyl chloride (59). Prepared according to the general procedure with 3-chloroanisole (157 mg, 1.10 mmol, 1.10 equiv) and 2-methoxybenzyl chloride (157 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (197 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 16.3, 7.9 Hz, 2H), 6.83 (s, 1H), 6.74 (s, 1H), 6.69 (s, 1H), 3.93 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.40, 157.49, 144.28, 134.70, 130.60, 128.79, 128.03, 121.68, 120.80, 113.71, 111.72, 110.72, 55.61, 55.57, 35.99. HRMS (EI+) calcd for $[C_{15}H_{15}ClO_2]^+$ m/z = 262.0760, found m/z = 262.0752.



Benzylation of 3-chloroanisole with 2-fluorobenzyl chloride (60). Prepared according to the general procedure with 3-chloroanisole (157 mg, 1.10 mmol, 1.10 equiv) and 2-fluorobenzyl chloride (145 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (223 mg, 89%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.08 (m, 2H), 6.84 (s, 1H), 6.78 (t, *J* = 1.9 Hz, 1H), 6.69 (s, 1H), 3.96 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.14, (*J* = 246 Hz), 160.61 , 142.98 , 135.04 , 131.26 (d, *J* = 4.5 Hz), 128.57 (d, *J* = 8.1 Hz), 127.30 (d, *J* = 15.9 Hz), 124.46 (d, *J* = 3.5 Hz), 121.50 , 115.69 (d, *J* = 21.9 Hz), 113.63 , 112.18 , 55.64 , 34.87 (d, *J* = 3.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.11. HRMS (EI+) calcd for $[C_{14}H_{12}ClFO]^+$ m/z = 250.0561, found m/z = 250.0576.

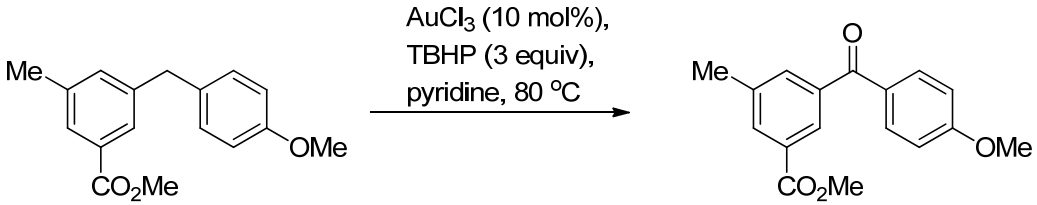


Benzylation of 3-chlorobenzonitrile with 2-methoxybenzyl chloride (61). Prepared according to the general procedure with 3-chloroanisole (152 mg, 1.10 mmol, 1.10 equiv) and 2-methoxybenzyl chloride (157 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (219 mg, 85%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.43 (s, 1H), 7.41 (d, J = 1.4 Hz, 1H), 7.30 (td, J = 7.9, 1.7 Hz, 1H), 7.15 (dd, J = 7.4, 1.6 Hz, 1H), 6.97 (td, J = 7.4, 1.0 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.98 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.46, 145.07, 135.06, 133.79, 130.88, 130.71, 129.48, 128.80, 127.34, 121.05, 118.04, 113.77, 111.00, 55.57, 35.97. HRMS (EI+) calcd for $[C_{15}H_{12}ClNO]^+$ m/z = 257.0607, found m/z = 257.0616.

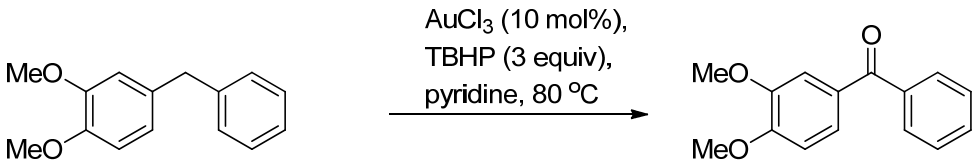


General Procedure for methylene oxidation of diarylmethanes to benzophenone derivatives. $AuCl_3$ (31 mg, 0.10 mmol, 0.10 equiv), diarylmethane (1.00 mmol, 1.00 equiv), TBHP (5.5 M in nonane, 0.55 mL, 3.0 mmol, 3.0 equiv) and pyridine (1 mL) were added to vial with a magnetic stir bar. The reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was cooled to room temperature, filtered through silica gel

washing with EtOAc, and concentrated under vacuum. The mixture was purified by flash column chromatography to give the product.

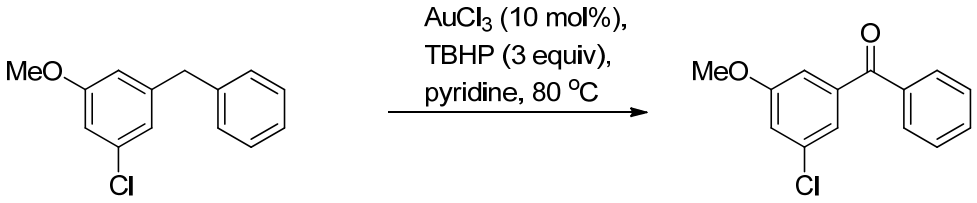


Oxidation of methyl 3-(4-methoxybenzyl)-5-methylbenzoate (62). Prepared according to the general procedure with methyl 3-(4-methoxybenzyl)-5-methylbenzoate (270 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (208 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.02 (s, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.93, 166.72, 163.65, 138.88, 138.85, 134.55, 133.56, 132.73, 130.27, 129.95, 128.20, 113.93, 55.72, 52.50, 21.43. HRMS (EI+) calcd for $[C_{17}H_{16}O_4]^+$ m/z = 284.1049, found m/z = 284.1058.

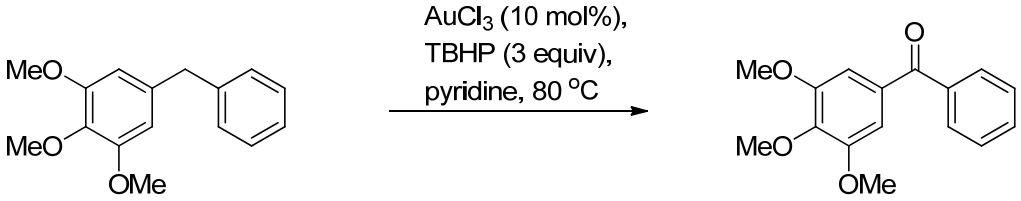


Oxidation of 4-benzyl-1,2-dimethoxybenzene (63). Prepared according to the general procedure with 1,2-dimethoxy-4-(4-methoxybenzyl)benzene (259 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (212 mg, 78%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.69 (d, J = 7.1 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (dd, J = 8.3, 1.9 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 195.60, 153.25, 149.21, 138.45, 132.03, 130.36, 129.84, 128.33, 125.65, 112.37, 110.04, 56.23, 56.17. HRMS (EI+) calcd for $[C_{15}H_{14}O_3]^+$ m/z = 242.0943, found m/z = 242.0948.

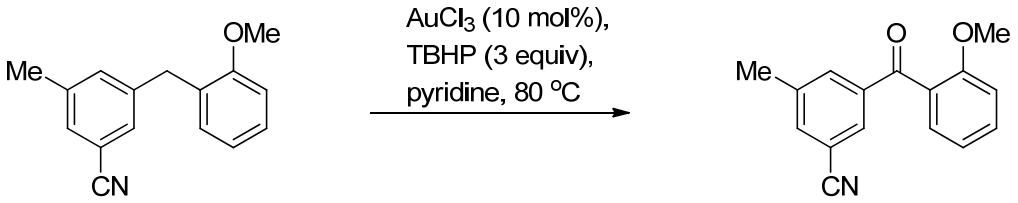


Oxidation of 1-benzyl-3-chloro-5-methoxybenzene (64). Prepared according to the general procedure with 1-benzyl-3-chloro-5-methoxybenzene (233 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (188 mg, 76%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.58 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.30 (m, 1H), 7.21 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.09 (t, *J* = 2.1 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.16, 160.44, 140.14, 137.15, 135.17, 133.02, 130.19, 128.64, 122.63, 118.62, 113.72, 55.98. HRMS (EI+) calcd for $[C_{14}H_{11}ClO_2]^+$ m/z = 246.0448, found m/z = 246.0449.

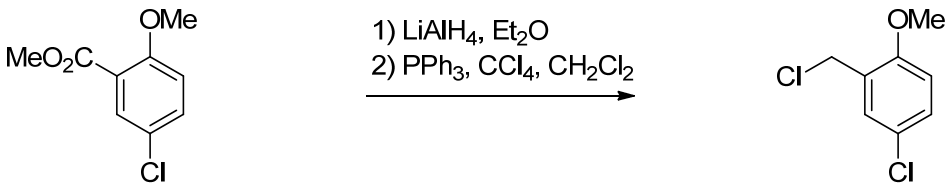


Oxidation of 5-benzyl-1,2,3-trimethoxybenzene (65). Prepared according to the general procedure with 5-benzyl-1,2,3-trimethoxybenzene (259 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (182 mg, 67%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.53 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.03 (s, 2H), 3.89 (s, 3H), 3.82 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.83, 153.08, 142.34, 138.00, 132.76, 132.45,

130.03, 128.45, 108.02, 61.11, 56.49. HRMS (EI+) calcd for $[C_{16}H_{16}O_4]^+$ m/z = 272.1049, found m/z = 272.1056.

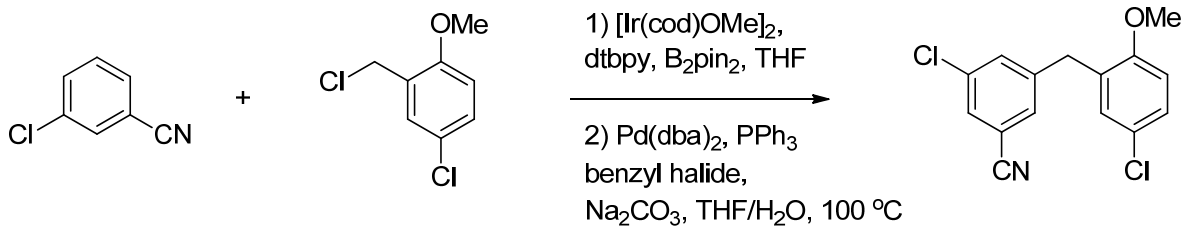


Oxidation of 3-(2-methoxybenzyl)-5-methylbenzonitrile (66). Prepared according to the general procedure with 3-(2-methoxybenzyl)-5-methylbenzonitrile (208 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (123 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 0.6 Hz, 1H), 7.77 (s, 1H), 7.60 (s, 1H), 7.51 (m, 1H), 7.38 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.06 (td, *J* = 7.5, 0.7 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 3.69 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.77, 157.65, 139.89, 139.12, 136.25, 134.16, 133.15, 131.03, 130.14, 127.69, 121.09, 118.54, 112.59, 111.83, 55.77, 21.33. HRMS (EI+) calcd for $[C_{16}H_{13}NO_2]^+$ m/z = 251.0946, found m/z = 251.0949.

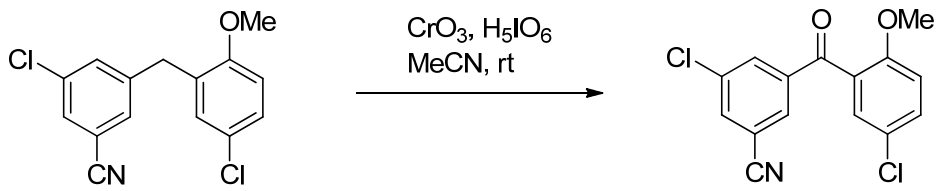


Synthesis of 2-methoxy-5-chlorobenzyl chloride. Inside a glove box, $LiAlH_4$ (760 mg, 20.0 mmol, 1.00 equiv) and dry Et_2O (30 mL) were added to a dry flask containing a magnetic stir bar. The flask was removed from the glove box and cooled to 0 °C. Methyl 5-chloro-2-methoxybenzoate (4.00 g, 20.0 mmol, 1.00 equiv) in 20 mL of dry Et_2O was added dropwise to the flask. The reaction mixture was allowed to warm to room temperature over 12 h. In succession, 1 mL H_2O, 0.5 mL 4 M NaOH (aq) and 3

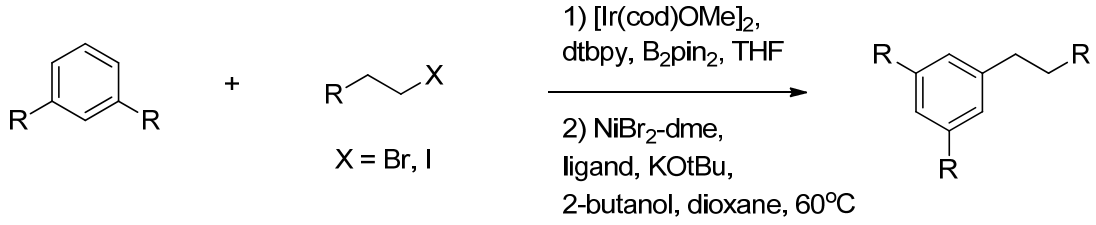
mL H_2O were added. The reaction mixture was filtered through Celite and $MgSO_4$, washing with Et_2O. The reaction mixture was concentrated and used in the next step without further purification. PPh_3 (10.5 g, 40.0 mmol, 2 equiv), CCl_4 (6.16 g, 40.0 mmol, 2.00 equiv) and CH_2Cl_2 (75 mL) were added to a dry flask and cooled to 0 °C. The crude product from the reduction step in 25 mL CH_2Cl_2 was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature over 8 h. After 8 h, the solvent was removed under vacuum and the product was purified by column chromatography (10% EtOAc: 90% hexanes) to give 2-methoxy-5-chlorobenzyl chloride. Spectral properties matched previously reported values.[28]



Coupling of 3-chlorobenzonitrile with 2-methoxy-5-chlorobenzyl chloride (67). Prepared according to the general procedure with 3-chlorobenzonitrile (152 mg, 1.10 mmol, 1.10 equiv) and 2-methoxy-5-chlorobenzyl chloride (191 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (208 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 6.0 Hz, 1H), 7.36 (s, 1H), 7.20 (dd, J = 8.7, 2.6 Hz, 1H), 7.07 (d, J = 2.5 Hz, 1H), 6.81 (s, 1H), 6.80 (s, 1H), 3.90 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.06, 144.09, 135.19, 133.71, 130.79, 130.39, 129.74, 129.09, 128.37, 125.72, 117.89, 113.89, 112.16, 55.93, 35.66. HRMS (EI+) calcd for $[C_{15}H_{11}Cl_2NO]^+$ m/z = 291.0218, found m/z = 291.0221.

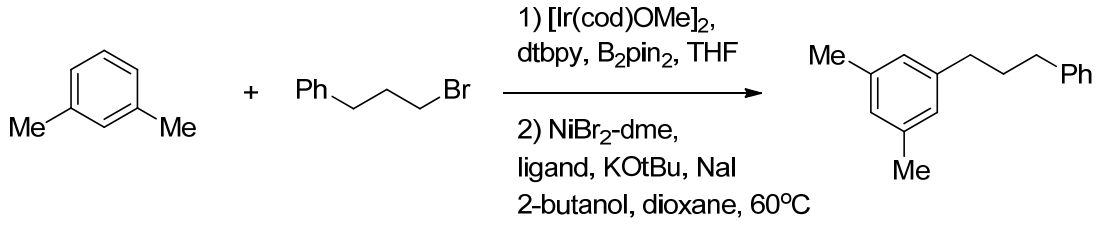


Oxidation of 3-chloro-5-(2-chloro-5-methoxybenzyl)benzonitrile to 3-chloro-5-(2-chloro-5-methoxybenzoyl)benzonitrile (68). CrO_3 (3 mg, 0.03 mol, 0.1 equiv) and H_5IO_6 (171 mg, 0.750 mmol, 2.5 equiv) were added to a vial containing a magnetic stir bar. 3-chloro-5-(2-chloro-5-methoxybenzyl)benzonitrile (88 mg, 0.3 mmol, 1.0 equiv) in MeCN (1.5 mL) was added and the reaction mixture was stirred at room temperature for 3 h. After 3 h, the reaction mixture was filtered through silica gel washing with EtOAc, and concentrated under vacuum. The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (67 mg, 73%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.86 (t, J = 1.4 Hz, 1H), 7.80 (m, 1H), 7.50 (dd, J = 8.9, 2.6 Hz, 1H), 7.39 (d, J = 2.6 Hz, 1H), 6.97 (s, 1H), 6.95 (s, 1H), 3.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.70, 156.22, 140.25, 135.95, 135.52, 133.58, 133.29, 131.40, 129.99, 128.17, 126.71, 116.92, 114.44, 113.37, 56.19. HRMS (EI+) calcd for $[C_{15}H_9Cl_2NO_2]^+$ m/z = 306.0089, found m/z = 306.0095.

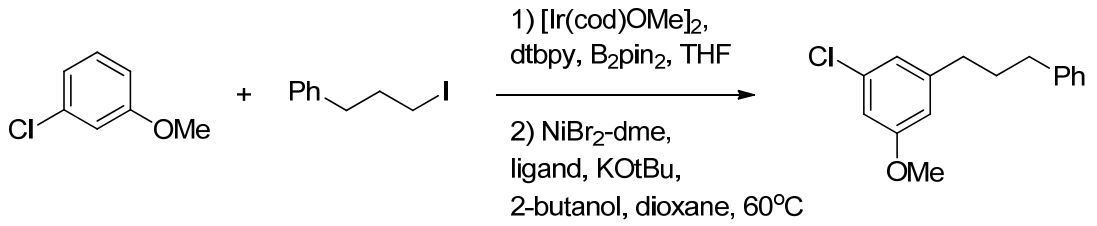


General Procedure for Alkylation of Arenes. Inside a glove box, $[Ir(cod)OMe]_2$ (2.5 mg, 0.0038 mmol, 0.0038 equiv), dtbpy (2.0 mg, 0.0075 mmol, 0.0075 equiv), B_2pin_2 (229 mg, 0.900 mmol, 0.900 equiv), arene (1.50 mmol, 1.50 equiv), and THF (3 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80

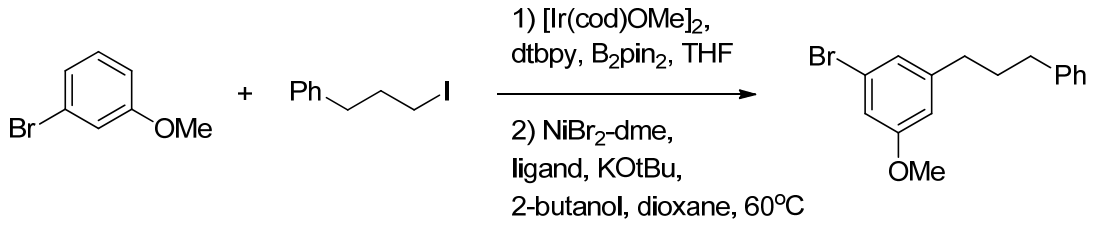
°C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $NiBr_2$-dme (30.9 mg, 0.100 mmol, 0.100 equiv), *trans*-*N*,*N*′-Dimethylcyclohexane-1,2-diamine (28.5 mg, 0.200 mmol, 0.200 equiv), the alkyl halide (1.00 mmol, 1.00 equiv), KOtBu (135 mg, 1.20 mmol, 1.20 equiv), 2-butanol (149 mg, 2.00 mmol, 2.00 equiv) and 1,4-dioxane (2 mL) were added consecutively to the reaction mixture. The reaction mixture was stirred at 60 °C for 15 hours. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.



Alkylation of *m*-xylene with 1-bromo-3-phenylpropane. Prepared according to the general procedure with *m*-xylene (159 mg, 1.50 mmol, 1.50 equiv), 1-bromo-3-phenylpropane (199 mg, 1.00 mmol, 1.00 equiv) and NaI (150 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (150 mg, 67%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 4H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.38 (s, 6H), 2.04 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.70, 142.53, 138.01, 128.74, 128.58, 127.68, 126.59, 126.00, 35.90, 35.66, 33.32, 21.59. HRMS (EI+) calcd for $[C_{17}H_{20}]^+$ m/z = 224.1565, found m/z = 224.1568.

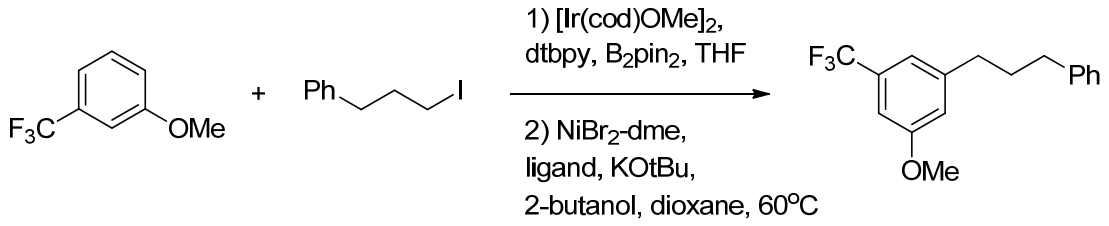


Alkylation of 3-chloroanisole with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 3-chloroanisole (213 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (216 mg, 83%). ^1H NMR (499 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.24 (m, 3H), 6.84 (s, 1H), 6.79 (s, 1H), 6.67 (s, 1H), 3.82 (s, 3H), 2.70 (t, J = 7.7 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.99 (p, J = 7.6, 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.55, 145.44, 142.21, 134.84, 128.70, 128.63, 126.13, 121.27, 113.23, 111.78, 55.66, 35.59, 35.51, 32.82. HRMS (EI+) calcd for $[C_{16}H_{17}ClO]^+$ m/z = 260.0968, found m/z = 260.0962.

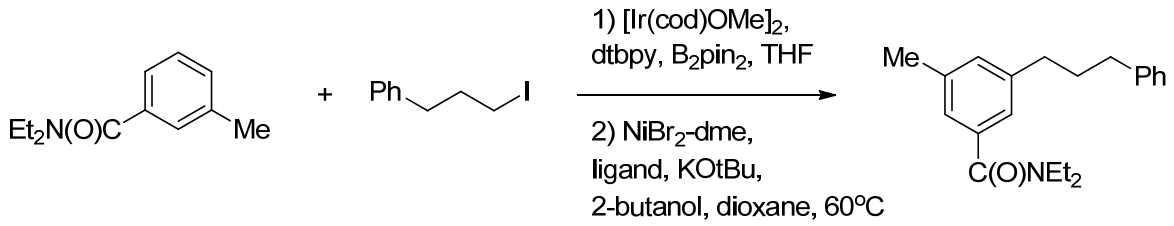


Alkylation of 3-bromoanisole with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 3-bromoanisole (281 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (216 mg, 71%). ^1H NMR (499 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.23 (m, 3H), 6.98 (s, 1H), 6.93 (s, 1H), 6.69 (s, 1H), 3.80 (s, 3H), 2.68 (t, J = 7.7 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H), 1.98 (tdd, J = 9.4, 6.9, 5.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.57, 145.75, 142.17, 128.68, 128.62,

126.11, 124.19, 122.86, 114.62, 113.75, 55.67, 35.57, 35.43, 32.82. HRMS (EI+) calcd for $[C_{16}H_{17}BrO]^+$ m/z = 304.0463, found m/z = 304.0470.

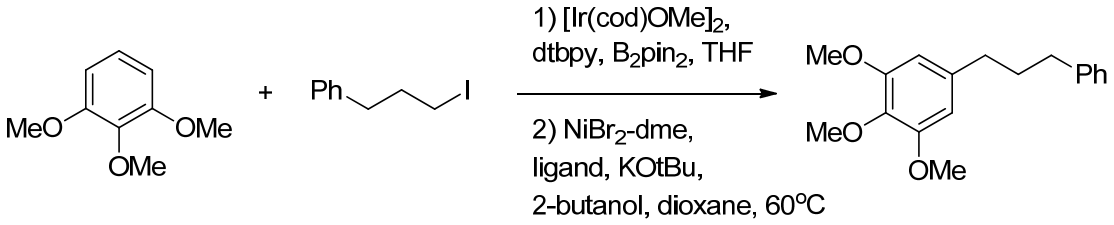


Alkylation of 3-(trifluoromethyl)anisole with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 3-(trifluoromethyl)anisole (265 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (201 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.25 (m, 3H), 7.10 (s, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 3.86 (s, 3H), 2.71 (m, 4H), 2.02 (tt, *J* = 9.2, 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.04, 145.10, 142.09, 131.91 (q, *J* = 31.8 Hz), 128.70, 128.65, 126.17, 124.39 (q, *J* = 273 Hz), 118.03, 117.80 (q, *J* = 3.8 Hz), 108.17 (q, *J* = 3.9 Hz), 55.64, 35.60, 35.56, 32.87. HRMS (EI+) calcd for $[C_{17}H_{17}F_3O]^+$ m/z = 294.1232, found m/z = 294.1240.

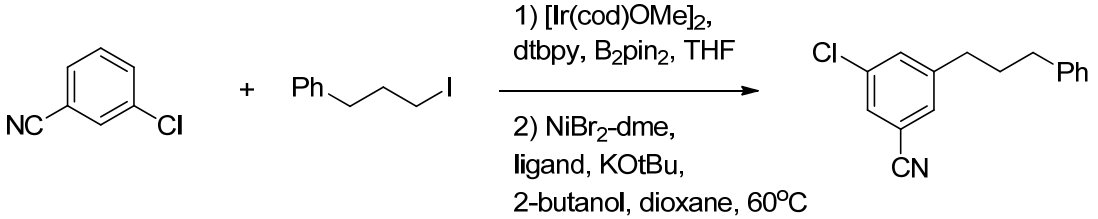


Alkylation of *N*,*N*-Diethyl-3-methylbenzamide with 1-iodo-3-phenylpropane. Prepared according to the general procedure with *N*,*N*-Diethyl-3-methylbenzamide (287 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85%

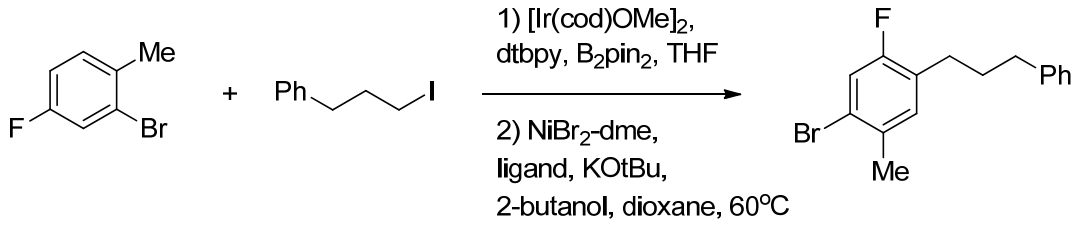
hexanes) to give the product (214 mg, 69%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 3H), 7.02 (m, 2H), 3.56 (m, 2H), 3.26 (m, 2H), 2.66 (dt, *J* = 10.6, 7.3 Hz, 4H), 2.35 (s, 3H), 1.97 (p, *J* = 7.8 Hz, 2H), 1.26 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.93, 142.66, 142.35, 138.32, 137.55, 130.23, 128.65, 128.56, 126.02, 124.59, 123.51, 43.53, 39.42, 35.70, 35.50, 33.08, 21.57, 14.49, 13.19. HRMS (EI+) calcd for $[C_{21}H_{27}NO]^+$ m/z = 309.2093, found m/z = 309.2100.



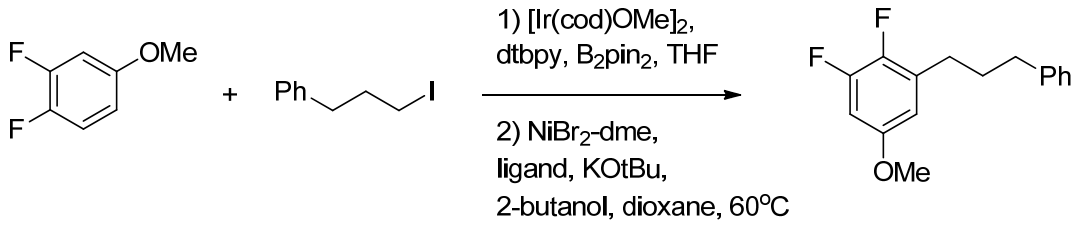
Alkylation of 1,2,3-trimethoxybenzene with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 1,2,3-trimethoxybenzene (252 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (143 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.21 (d, *J* = 6.8 Hz, 3H), 6.41 (s, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.29, 142.41, 138.29, 128.68, 128.56, 126.03, 122.67, 105.51, 61.09, 56.29, 36.09, 35.72, 33.19. HRMS (EI+) calcd for $[C_{18}H_{22}O_3]^+$ m/z = 286.1569, found m/z = 286.1565.



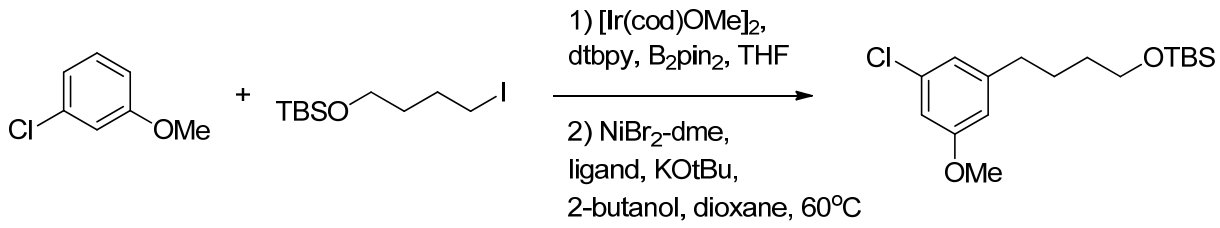
Alkylation of 3-chlorobenzonitrile with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 3-chlorobenzonitrile (207 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (182 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (m, 1H), 7.18 (m, 2H), 2.66 (td, *J* = 7.8, 2.8 Hz, 4H), 1.96 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.89, 141.46, 135.25, 133.51, 130.51, 129.55, 128.73, 128.61, 126.35, 117.89, 113.95, 35.40, 34.88, 32.52. HRMS (EI+) calcd for $[C_{16}H_{14}ClN]^+$ m/z = 255.0815, found m/z = 255.0809.



Alkylation of 2-bromo-4-fluorotoluene with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 2-bromo-4-fluorotoluene (284 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (234 mg, 76%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.7, 6.5 Hz, 2H), 7.22 (m, 4H), 7.05 (d, *J* = 7.8 Hz, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.35 (s, 3H), 1.94 (tt, *J* = 9.6, 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.24 (d, *J* = 246.7 Hz), 142.13 , 133.46 (d, *J* = 3.6 Hz), 132.29 (d, *J* = 5.5 Hz), 128.61 (d, *J* = 6.1 Hz), 128.38 (d, *J* = 16.0 Hz), 126.09, 121.66 (d, *J* = 9.7 Hz), 119.42, 119.22, 35.69, 31.78, 28.60, 22.20. ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.48. HRMS (EI+) calcd for $[C_{16}H_{16}BrF]^+$ m/z = 306.0419, found m/z = 306.0422.

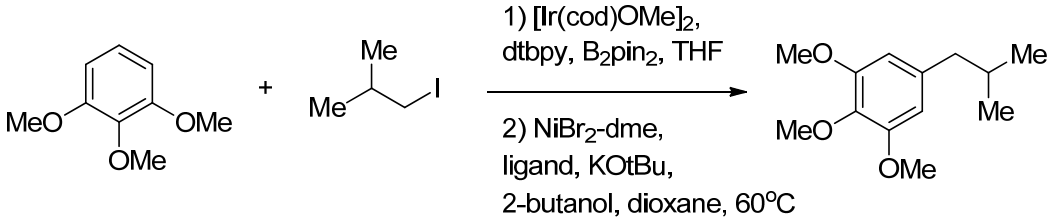


Alkylation of 3,4-difluoroanisole with 1-iodo-3-phenylpropane. Prepared according to the general procedure with 3,4-difluoroanisole (216 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-3-phenylpropane (246 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (181 mg, 69%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.20 (m, 3H), 6.56 (ddd, *J* = 11.8, 6.2, 3.1 Hz, 1H), 6.46 (dd, *J* = 3.9, 1.7 Hz, 1H), 3.75 (s, 3H), 2.68 (t, *J* = 7.7 Hz, 4H), 1.96 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.35 (d, *J* = 11.1 Hz), 150.816 (dd, J = 14.6 Hz, 247.2 Hz), 143.75 (dd, *J* = 12.9 Hz, 238.9 Hz), 142.02 , 131.86 (d, *J* = 13.8 Hz), 128.61 (d, *J* = 4.9 Hz), 126.11, 123.02, 110.28, 100.96 (d, *J* = 20.8 Hz), 56.01, 35.61, 31.70, 29.05. ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.05 (dd, *J* = 21.5, 11.7 Hz), -154.47 (d, *J* = 21.8 Hz). HRMS (EI+) calcd for $[C_{16}H_{16}FO]^+$ m/z = 262.1169, found m/z = 262.1175.

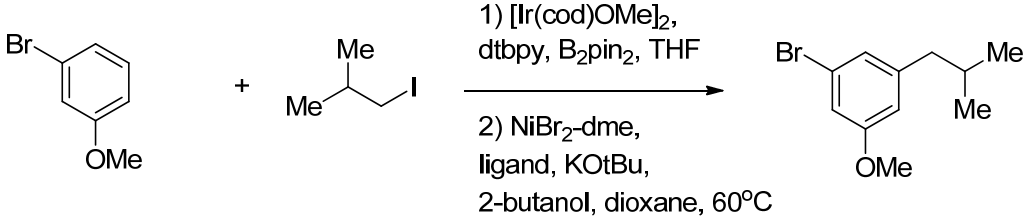


Alkylation of 3-chloroanisole with *tert*-Butyl(4-iodobutoxy)dimethylsilane. Prepared according to the general procedure with 3-chloroanisole (213 mg, 1.50 mmol, 1.50 equiv) and *tert*-Butyl(4-iodobutoxy)dimethylsilane (315 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (169 mg, 52%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 1.6 Hz, 1H), 6.73

(d, J = 2.0 Hz, 1H), 6.62 (d, J = 1.9 Hz, 1H), 3.78 (s, 3H), 3.64 (m, 2H), 2.58 (t, J = 7.6 Hz, 2H), 1.66 (m, 2H), 1.56 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.45, 145.73, 134.72, 121.21, 113.10, 111.63, 63.10, 55.57, 35.75, 32.50, 27.55, 26.22, 18.59, -5.04. HRMS (EI+) calcd for $[C_{16}H_{26}ClO_2Si]^+$ $(M\text{-}CH_3)^+$ m/z = 313.1391, found m/z = 313.1383.

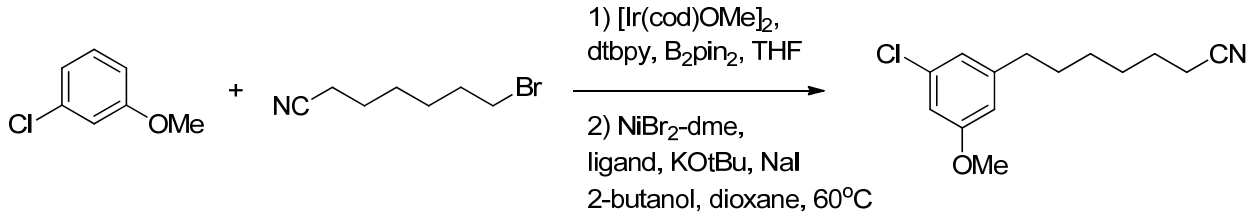


Alkylation of 1,2,3-trimethoxybenzene with 1-iodo-2-methylpropane. Prepared according to the general procedure with 1,2,3-trimethoxybenzene (252 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-2-methylpropane (184 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% Et_2O:85% pentane) to give the product (114 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (s, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 2.41 (d, J = 7.3 Hz, 2H), 1.85 (hept, J = 6.8 Hz, 1H), 0.91 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.08, 137.75, 122.91, 106.14, 61.08, 56.25, 46.11, 30.51, 22.66. HRMS (EI+) calcd for $[C_{13}H_{20}O_3]^+$ m/z = 224.1413, found m/z = 224.1410.

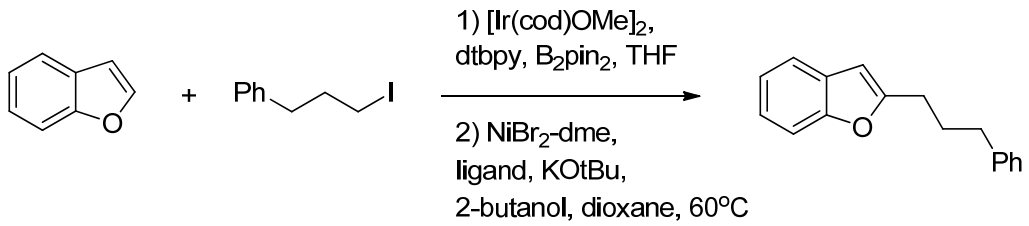


Alkylation of 3-bromoanisole with 1-iodo-2-methylpropane. Prepared according to the general procedure with 3-bromoanisole (281 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-2-methylpropane (184 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash

column chromatography (5% Et_2O:95% pentane) to give the product (121 mg, 50%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (t, *J* = 1.6 Hz, 1H), 6.89 (t, *J* = 2.1 Hz, 1H), 6.62 (dd, *J* = 2.4, 1.4 Hz, 1H), 3.78 (s, 3H), 2.41 (d, *J* = 7.2 Hz, 2H), 1.86 (hept, *J* = 7.0 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.35, 145.15, 124.77, 122.60, 114.40, 114.35, 55.61, 45.39, 30.27, 22.55. HRMS (EI+) calcd for $[C_{11}H_{15}BrO]^+$ m/z = 242.0306, found m/z = 242.0298.

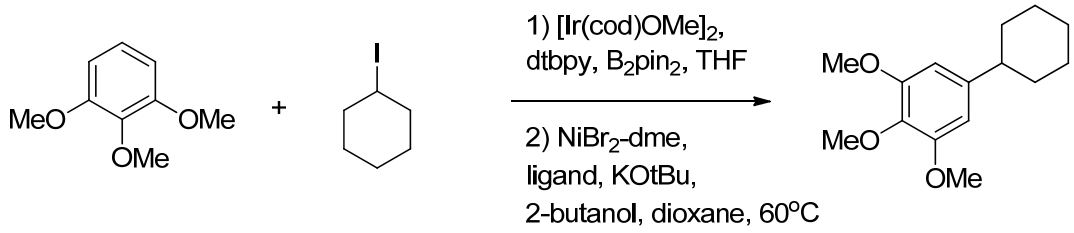


Alkylation of 3-chloroanisole with 7-bromoheptanenitrile. Prepared according to the general procedure with 3-chloroanisole (213 mg, 1.50 mmol, 1.50 equiv), 7-bromoheptanenitrile (190 mg, 1.00 mmol, 1.00 equiv), and NaI (150 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% Et_2O:90% pentane) to give the product (149 mg, 59%). ^1H NMR (499 MHz, $CDCl_3$) δ 6.76 (t, *J* = 1.7 Hz, 1H), 6.73 (t, *J* = 2.1 Hz, 1H), 6.60 (t, *J* = 1.9 Hz, 1H), 3.79 (s, 3H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.64 (m, 4H), 1.48 (m, 2H), 1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.50, 145.47, 134.77, 121.13, 119.96, 113.13, 111.68, 55.65, 35.81, 30.92, 28.71, 28.50, 25.50, 17.34. HRMS (EI+) calcd for $[C_{14}H_{18}ClNO]^+$ m/z = 251.1077, found m/z = 251.1074.

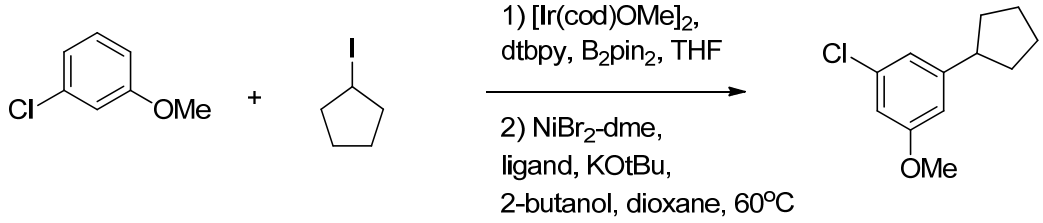


Alkylation of benzofuran with 1-iodo-3-phenylpropane. Prepared according to the general procedure with benzofuran (177 mg, 1.50 mmol, 1.50 equiv) and 1-iodo-2-methylpropane (184 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (114 mg, 51%). ^1H NMR (500 MHz, Chloroform-d) δ 7.53 (d, *J* = 7.0 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.25 (m, 5H), 6.44 (s, 1H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.13 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.37, 154.92, 141.98, 129.20, 128.77, 128.65, 126.19, 123.40, 122.68, 120.48, 111.00, 102.38, 35.48, 29.54, 28.15.

General Procedure for Alkylation of Arenes with Secondary Alkyl Halides. Inside a glove box, $[Ir(cod)OMe]_2$ (2.5 mg, 0.0038 mmol, 0.0038 equiv), dtbpy (2.0 mg, 0.0075 mmol, 0.0075 equiv), B_2pin_2 (229 mg, 0.900 mmol, 0.900 equiv), arene (1.50 mmol, 1.50 equiv), and THF (3 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $NiBr_2$-dme (30.9 mg, 0.100 mmol, 0.100 equiv), bathophenanthroline (66.5 mg, 0.200 mmol, 0.200 equiv), the alkyl halide (1.00 mmol, 1.00 equiv), KOtBu (135 mg, 1.20 mmol, 1.20 equiv), 2-butanol (149 mg, 2.00 mmol, 2.00 equiv) and 1,4-dioxane (2 mL) were added consecutively to the reaction mixture. The reaction mixture was stirred at 60 °C for 15 hours. The reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

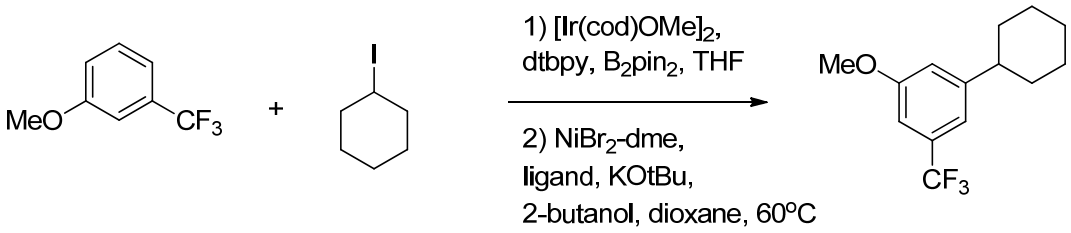


Alkylation of 1,2,3-trimethoxybenzene with iodocyclohexane. Prepared according to the general procedure with 1,2,3-trimethoxybenzene (252 mg, 1.50 mmol, 1.50 equiv) and iodocyclohexane (210 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% Et_2O:85% pentane) to give the product (184 mg, 74%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 2.44 (ddt, *J* = 11.2, 7.1, 3.6 Hz, 1H), 1.85 (m, 4H), 1.75 (m, 1H), 1.39 (m, 3H), 1.26 (qt, *J* = 11.6, 7.5, 6.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.22, 144.24, 128.55, 103.86, 61.04, 56.24, 45.28, 34.85, 27.13, 26.37. HRMS (EI+) calcd for $[C_{15}H_{22}O_3]^+$ m/z = 250.1569, found m/z = 250.1566.

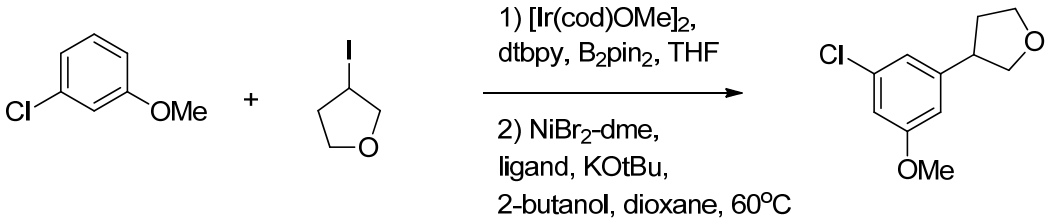


Alkylation of 3-chloroanisole with iodocyclopentane. Prepared according to the general procedure with 3-chloroanisole (213 mg, 1.50 mmol, 1.50 equiv) and iodocyclopentane (196 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (169 mg, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (m, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 3.78 (s, 3H), 2.93 (m, 1H), 2.05 (m, 2H), 1.80 (td, *J* = 6.6, 6.2, 3.4 Hz, 2H), 1.67 (m, 2H), 1.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.38, 149.84, 134.69, 119.97,

112.08, 111.35, 55.63, 46.01, 34.58, 25.66. HRMS (EI+) calcd for $[C_{12}H_{15}ClO]^+$ m/z = 210.0812, found m/z = 210.0804.

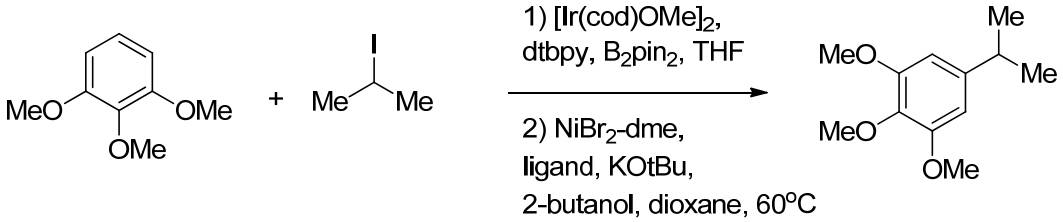


Alkylation of 3-(trifluoromethyl)anisole with iodocyclohexane. Prepared according to the general procedure with 3-(trifluoromethyl)anisole (264 mg, 1.50 mmol, 1.50 equiv) and iodocyclohexane (210 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% Et_2O:95% pentane) to give the product (141 mg, 55%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.96 (s, 1H), 6.94 (s, 1H), 3.85 (s, 3H), 2.55 (m, 1H), 1.88 (qd, *J* = 8.5, 7.1, 3.7 Hz, 4H), 1.78 (m, 1H), 1.42 (m, 4H), 1.29 (ddt, *J* = 13.3, 7.8, 3.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.97, 150.86, 131.76 (q, *J* = 31.8 Hz), 124.42 (q, *J* = 272.5 Hz), 116.63, 116.31 (q, *J* = 3.8 Hz), 107.89 (q, *J* = 3.8 Hz), 55.61, 44.81, 34.46, 26.95, 26.24. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.99. HRMS (EI+) calcd for $[C_{14}H_{17}F_3O]^+$ m/z = 258.1232, found m/z = 258.1224.

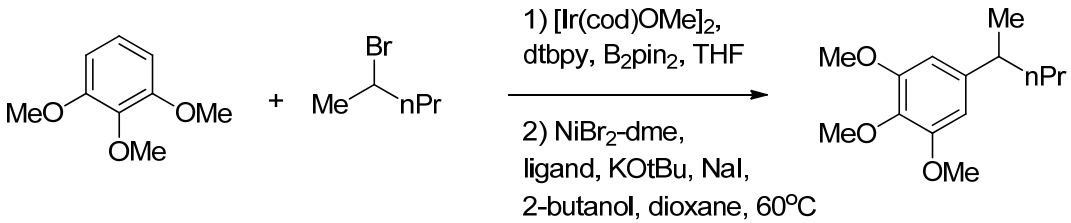


Alkylation of 3-chloroanisole with 3-iodotetrahydrofuran. Prepared according to the general procedure with 3-chloroanisole (213 mg, 1.50 mmol, 1.50 equiv) and 3-iodotetrahydrofuran (198 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash

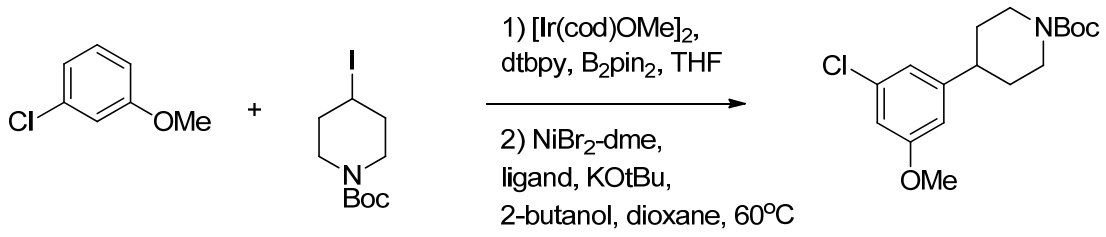
column chromatography (5% Et_2O:95% pentane) to give the product (171 mg, 81%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 4.06 (m, 2H), 3.88 (m, 1H), 3.78 (s, 1H), 3.70 (m, 1H), 3.33 (h, J = 7.7, 6.9 Hz, 1H), 2.34 (dtd, J = 12.5, 7.8, 4.5 Hz, 1H), 1.96 (dq, J = 12.2, 7.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.61, 146.12, 135.10, 119.97, 112.20, 104.69, 74.53, 68.62, 55.70, 45.00, 34.63. HRMS (EI+) calcd for $[C_{11}H_{13}ClO_3]^+$ m/z = 212.0604, found m/z = 212.0611.



Alkylation of 1,2,3-trimethoxybenzene with 2-iodopropane. Prepared according to the general procedure with 1,2,3-trimethoxybenzene (252 mg, 1.50 mmol, 1.50 equiv) and 2-iodopropane (170 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% Et_2O:85% pentane) to give the product (107 mg, 51%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 2.84 (hept, J = 6.9 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.25, 144.99, 136.12, 103.44, 61.06, 56.25, 34.79, 24.34. HRMS (EI+) calcd for $[C_{12}H_{18}O_3]^+$ m/z = 210.1256, found m/z = 210.1264.



Alkylation of 1,2,3-trimethoxybenzene with 2-bromopentane. Prepared according to the general procedure with 1,2,3-trimethoxybenzene (252 mg, 1.50 mmol, 1.50 equiv), 2-bromopentane (151 mg, 1.00 mmol, 1.00 equiv), and NaI (150 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% Et_2O:85% pentane) to give the product (152 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 2.62 (h, *J* = 7.0 Hz, 1H), 1.51 (m, 2H), 1.27 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.88 (td, *J* = 7.3, 1.0 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.20, 144.11, 136.09, 103.92, 61.06, 56.25, 41.00, 40.38, 22.51, 21.08, 14.40. HRMS (EI+) calcd for $[C_{14}H_{22}O_3]^+$ m/z = 238.1569, found m/z = 238.1578.



Alkylation of 3-chloroanisole with N-Boc-4-iodopiperidne. Prepared according to the general procedure with 3-chloroanisole (213 mg, 1.50 mmol, 1.50 equiv) and N-Boc-4-iodopiperidine (312 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexane) to give the product (176 mg, 54%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.74 (s, 1H), 6.63 (s, 1H), 4.23 (s, 2H), 3.78 (s, 3H), 2.77 (s, 2H), 2.57 (dt, *J* = 13.4, 4.2 Hz, 1H), 1.79 (m, 2H), 1.57 (tt, *J* = 12.4, 6.3 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.60, 154.99, 148.92, 135.00, 119.67, 112.05, 111.73, 79.75, 55.65, 42.87, 33.15, 28.70. HRMS (EI+) calcd for $[C_{17}H_{24}ClNO_3]^+$ m/z = 325.1445, found m/z = 325.1437.

3.6 References

(1) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

(2) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(3) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(4) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(5) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792.

(6) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

(7) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.

(8) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761.

(9) a) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem. Int. Ed.* **2012**, *51*, 540;
b) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 536.

(10) a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593; b) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090; c) Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 4455.

(11) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072.

(12) Pigge, F. C. *Synthesis* **2010**, *2010*, 1745.

(13) Ortar, G. *Tetrahedron Lett.* **2003**, *44*, 4311.

(14) a) Burns, M. J.; Fairlamb, I. J. S.; Kapdi, A. R.; Sehnal, P.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 5397; b) Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, *2003*, 1668;
c) Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 4121; d) López-Pérez, A.;

Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514; e) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198; f) Nobre, S. M.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225.

(15) a) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966; b) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160; c) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360.

(16) Vougioukalakis, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 2234.

(17) Rossi, P.-G.; Bao, L.; Luciani, A.; Panighi, J.; Desjobert, J.-M.; Costa, J.; Casanova, J.; Bolla, J.-M.; Berti, L. *J. Agric. Food Chem.* **2007**, *55*, 7332.

(18) Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.-G.; Podesta, J. C. *Eur. J. Org. Chem.* **2009**, 3964.

(19) Li, H.; Li, Z.; Shi, Z. *Tetrahedron* **2009**, *65*, 1856.

(20) Romines, K. R.; Freeman, G. A.; Schaller, L. T.; Cowan, J. R.; Gonzales, S. S.; Tidwell, J. H.; Andrews, C. W., III; Stammers, D. K.; Hazen, R. J.; Ferris, R. G.; Short, S. A.; Chan, J. H.; Boone, L. R. *J. Med. Chem.* **2006**, *49*, 727.

(21) a) Yamazaki, S. *Org. Lett.* **1999**, *1*, 2129; b) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.

(22) a) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360; b) Lu, Z.; Fu, G. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6676; c) Molander, G. A.; Argintaru, O. A.; Aron, I.; Dreher, S. D. *Org. Lett.* **2010**, *12*, 5783; d) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525; e) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602; f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

(23) Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 3904.

(24) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674.

(25) a) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154; b) Li, Z.; Jiang, Y.-Y.; Fu, Y. *Chem. Eur. J.* **2012**, n/a; c) Hu, X. *Chem. Sci.* **2011**, *2*, 1867.

(26) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073.

(27) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

(28) R. Pfleger and K. Waldmann`, Chem. Ber.`, 90`, 2395 (1957)

Chapter 4. A C-H Borylation Approach to Suzuki-Miyaura Coupling of Typically Unstable 2-Heteroaryl and Polyfluorophenyl Boronates with Simple Catalysts

4.1 Introduction

Suzuki-Miyaura cross coupling is one of the most utilized methods for the construction of carbon-carbon bonds.[1] Suzuki-Miyaura coupling has been utilized to construct molecules with a variety of functions, including pharmaceutical agents, natural products, and functional materials (Figure 1). The Suzuki-Miyaura coupling reaction has found widespread use because of several attractive features, including mild conditions, tolerance of a variety of functional groups, the ease of synthesis of organoboron compounds, and widespread access to a variety of coupling partners. Highly active catalysts have been developed for Suzuki-Miyaura cross-coupling and these catalysts have enabled for Suzuki coupling to be conducted with less reaction electrophiles, such as aryl chlorides and sulfonates, as well as with a wide variety of organoboron compounds.[2]

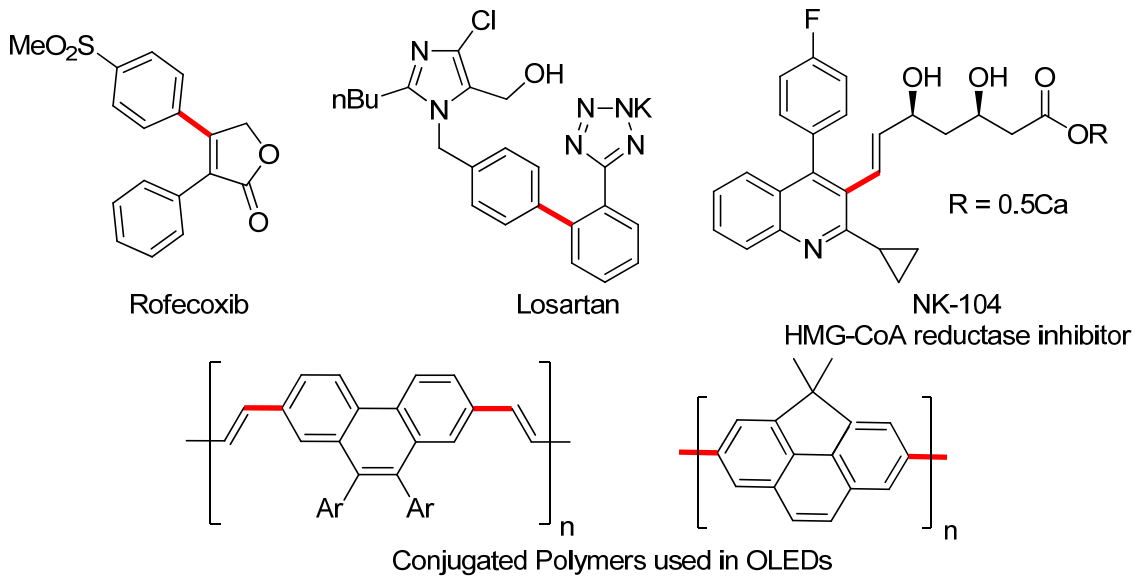


Figure 1. Large-scale applications of Suzuki-Miyaura coupling; the bond made by Pd-catalyzed Suzuki-Miyaura coupling is highlighted in red

4.2 Background

Despite the broad utility of Suzuki-Miyaura cross-coupling, coupling with several classes of organoboron compounds, such as 2-heteroaryl and polyfluoroaryl boronates, are challenging because the boronic acids are unstable to protodeborylation. Several approaches to enable cross coupling of these classes of organoboronates have been reported (Figure 2). By one approach, the boronic acid is converted to a boronic acid derivative, such as a trifluoroborate salt,[3] a cyclic triolborate,[4] a lithium borate salt[5] or a MIDA boronate (MIDA = *N*-methyliminodiacetic acid).[6] The protected organoboronate is then hydrolyzed *in situ* to the boronic acid, which participates in the cross-coupling reaction. These approaches require initial synthesis of the unstable boronic acid, often via lithiation of an arene or heteroarene at low temperatures. By a second approach, the coupling step is conducted with a highly active metallacyclic palladium catalyst bearing an expensive specialized biarylmonophosphine ligand to ensure that the coupling reaction

is faster than protodeborylation.[7] While this approach furnishes good yields for the coupling products, it does not address the problem of isolating, handling, and storing the boronic acid.

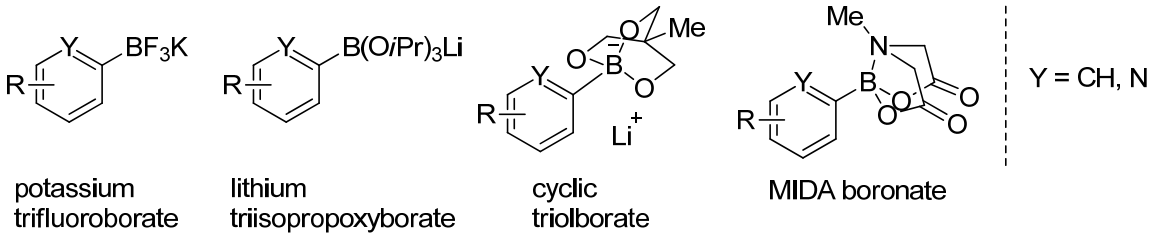
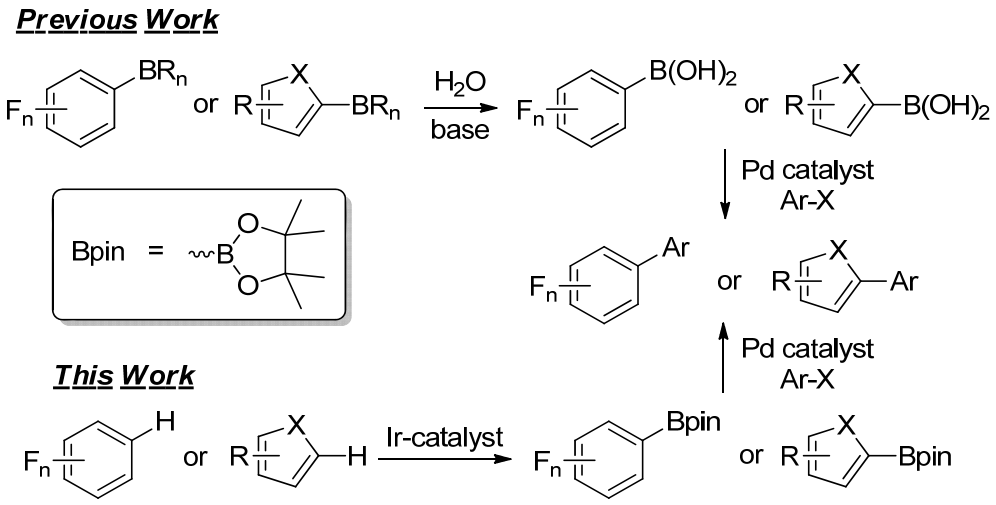


Figure 2. Boronic acid surrogates for Suzuki coupling of unstable boronates

We considered that this synthetic problem could be addressed by exploiting the borylation of arenes and heteroarenes to form pinacol-substituted organoboronic esters (Scheme 45). Recent mechanistic studies of the Suzuki-Miyaura reaction[8] imply that transmetallation of a neutral organoboron compound occurs with a pinacol boronate ester under mild conditions without the intermediacy of the boronic acid, even at -55 °C. In addition, we hypothesized that pinacol boronate esters formed by C-H borylation[9] would be sufficiently stable to protodeborylation in pure form and in solution, due to the increased electron density and steric hindrance around the boron atom in these compounds.[10] In addition, we envisioned that simple palladium catalysts could be identified for the cross coupling of these more stable pinacol boronate esters with aryl bromides.



Scheme 45. Approaches to Suzuki-Miyaura cross-coupling of unstable organoboronates

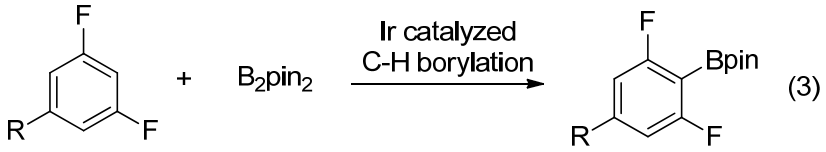
We report a general, one-pot method for arylation of heteroarenes and fluorinated arenes by Ir-catalyzed C-H borylation, followed by Pd-catalyzed cross-coupling with pinacol boronate esters as surrogates for unstable boronic acids. This method rests upon the simplicity of forming pinacol boronates by C-H borylation chemistry that creates gaseous H_2 as the sole byproduct, the enhanced stability of pinacol boronates, relative to their corresponding boronic acids, and the rapid transmetallation of the resulting pinacol boronates with palladium complexes bearing simple phosphine ligands.

4.3 Results and Discussion

We chose to address the challenge of the Suzuki-Miyaura coupling of 2-heteroaryl boronates and polyfluoroaryl boronates because these aromatic groups are common substructures in medicinal chemistry but have been difficult to introduce by cross coupling. While these classes of (hetero)aryl pinacol boronates can be synthesized by lithation of an aryl bromide, followed by quenching with an alkoxyborate, or by the catalytic borylation of aryl halides, the borylation of the arene or heteroarene itself is a direct method to access these pinacol boronates.[11] Although this reaction has been

reported previously, we found that the products from these reactions are stable both in the solid state and in solution. This stability enables the strategy for Suzuki coupling of unstable boronates with simple catalysts. While the isolated yields of the pinacol boronates are generally moderate to good, previous work has demonstrated that the GC yield of the pinacol boronate in the crude reaction mixture following the C-H borylation reaction is high,[12] indicating that a method to utilize these boronates *in situ* could potentially be advantageous.

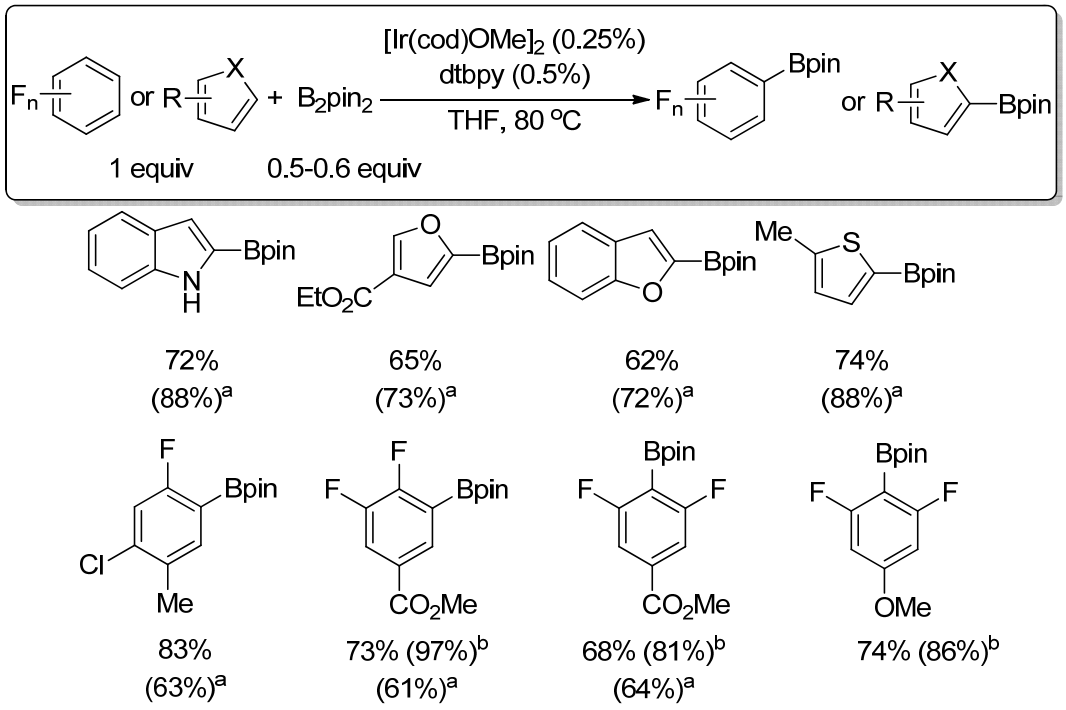
Mono- and di-*ortho*-fluoroaryl pinacol boronates also form by iridium-catalyzed C-H borylation and are stable both in the solid state and in solution. Because the regioselectivity of the C-H borylation of arenes occurs at the least hindered C-H bond, we hypothesized that the reaction of a 3,5-difluoroarene with B_2pin_2 or HBpin in the presence of the same Ir catalyst would yield a 2,6-difluoroaryl pinacol boronate, as shown in Equation 3. This borylation occurs at the C-H bond *ortho* to both fluorine atoms due to the small size of fluorine. Indeed, the borylation of polyfluorinated arenes occurred *ortho* to the fluorine atom with 0.6 equivalents of B_2pin_2 or 1.1 equivalents of HBpin as the boron source (Table 11). These reactions occur with 3,5-difluoroarenes containing electron-donating or electron-withdrawing substituents. They also occur with 3,4-difluoroarenes to form a single arylboronate ester. Similar to 2-heteroaryl pinacol boronates, these fluoroarylpinacol boronate esters demonstrate sufficient stability to silica gel chromatography to allow for convenient laboratory purification, but some of the pinacol boronate ester is lost during isolation. However, GC yields of the borylation product from the crude reaction mixture are high, indicating that a method to utilize these boronates *in situ* could developed.



(3)

These heteroaryl and fluoroaryl pinacol boronates are stable indefinitely on the bench top. Unlike the corresponding boronic acids, both the 2-heteroaryl and polyfluoroaryl pinacol boronate esters are stable in air at room temperature for at least 60 days without decomposition. Because these compounds can be stored and used without the need for cryogenic or anaerobic conditions, which is often necessary for handling these classes of boronic acids, the corresponding pinacol boronate esters should be useful building blocks for the synthesis of complex molecules with a variety of functions.

Table 11. Iridium-catalyzed borylation of heteroarenes and polyfluorobenzene derivatives



[a]Isolated yield obtained when 1.1 equiv. of HBpin was used as the boron source; [b]GC yield

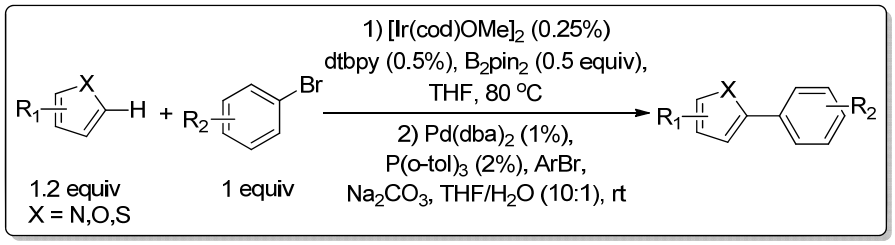
If the stability of these boronates is to be an asset, however, they must undergo cross coupling under mild conditions with accessible catalysts. After examining several catalyst and ligand combinations, we found that the classic catalyst generated from 1 mol % $Pd(dba)_2$ and 2 mol % P(*o*-tol)$_3$ with Na_2CO_3 as base in a 10:1 mixture of THF:H_2O led to the coupling of these organoboronates with a variety of aryl bromides at room temperature.[13]

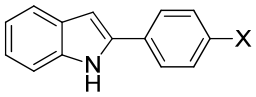
With a suitable catalyst and reaction conditions for the Suzuki-Miyaura coupling of 2-heteroaryl boronates with aryl bromides in hand, we developed a one-pot process for Ir-catalyzed heteroarene C-H borylation and Pd-catalyzed coupling. The scope of this sequence is shown in Table 12. A variety of heterocycles, including pyrroles, indoles, furans, benzofurans and thiophenes containing a variety of substituents underwent the borylation and coupling with a series of electron-rich and electron-poor aryl and heteroaryl bromides. In addition, *ortho*-substituted and *ortho*-di-substituted aryl bromides reacted with the intermediate heteroarylboronic ester in good yield. Esters, aldehydes, aryl halides, trifluoromethyl groups, as well as ketones with enolizable hydrogens, were well tolerated. Silylated phenols, MOM-protected hydroxyalkylarenes, and an aryl pivalate, which can be used for orthogonal Ni-catalyzed cross-coupling,[14] also underwent the one-pot sequence in good yield. Because aryl bromides are most commonly utilized in medicinal chemistry, this method for Suzuki coupling of heteroaryl pinacol boronates with aryl bromides using simple Pd catalysts should be widely utilized.

In addition to the coupling of 2-heteroaryl boronates with aryl bromides, *ortho*-fluoro pinacol boronate esters were also coupled with aryl bromides. With appropriate substitution on the starting fluoroarene, the borylation occurs with site-selectivity *ortho* to

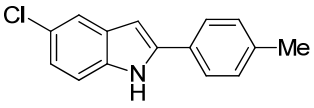
fluorine, and these resulting pinacol boronate esters were coupled with a variety of aryl bromides at room temperature in the presence of the Pd/P(*o*-tol)$_3$ catalyst.

Table 12. Scope of the combined Ir-catalyzed borylation and Pd-catalyzed cross coupling of heteroarenes with aryl bromides

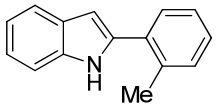




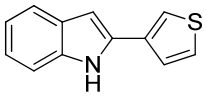
X = Me; 84%
X = C(O)Me; 55%
X = CO_2Et; 87%



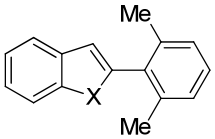
78%



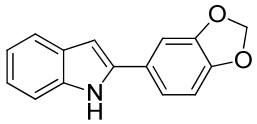
73%



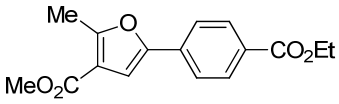
70%



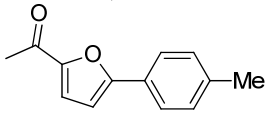
X = NH; 72%[a]
X = O; 65%[a]



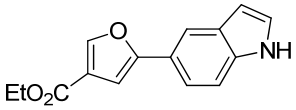
84%



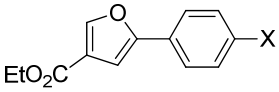
97%



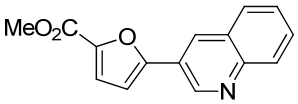
69%



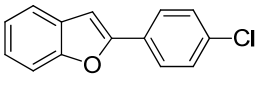
88%[a]



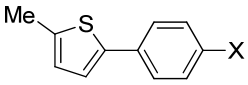
X = Cl; 89%
X = OPiv; 80%



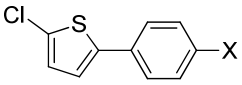
96%[a]



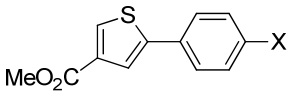
85%



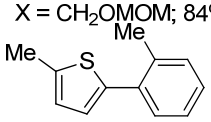
X = Me; 91%
X = OMe; 84% (80%[b])
X = C(O)Me; 90%
X = CHO; 93%
X = CH_2OMOM; 84%



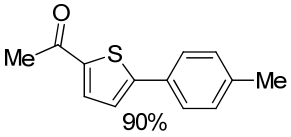
X = Me; 92%
X = NMe_2; 78%
X = CN; 85%



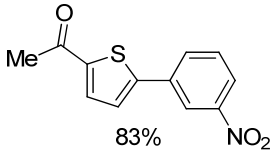
X = CHO; 83%
X = Me; 95%
X = OTBS; 96%



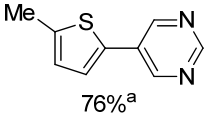
96%



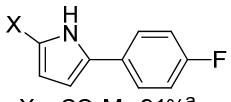
90%



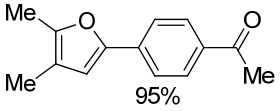
83%



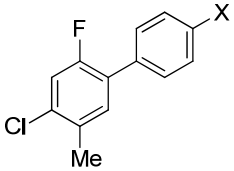
76%[a]



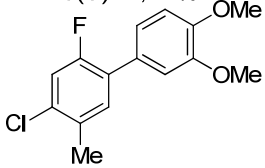
X = CO_2Me;91%[a]
X = C(O)Me; 75%[a]



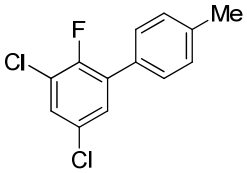
95%



X = Cl; 96%
X = C(O)Me; 85%
X = CO_2Et; 81%



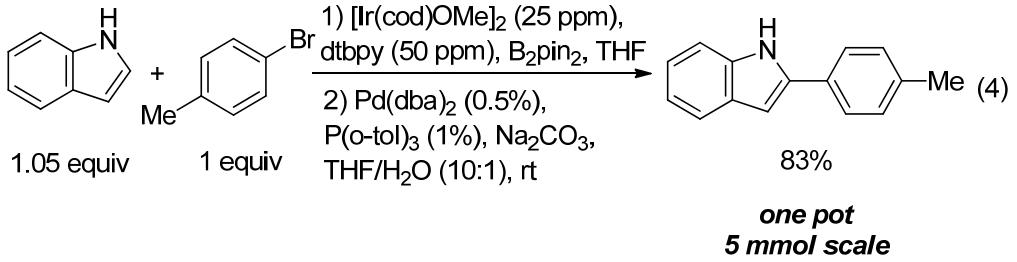
99%



95%

[a]Pd-catalyzed coupling at 50°C; [b]Borylation/coupling sequence conducted without use of a glovebox

In addition to occurring with broad scope, the combination of heteroarene borylation and cross coupling occurred on a 5 mmol scale with lower catalyst loadings than the reactions on smaller scale (Equation 4). The borylation of indole on 5 mmol scale was performed with 50 ppm of iridium catalyst, and the subsequent coupling with 4-bromotoluene occurred with 0.5 mol % of the palladium catalyst in similar yield to the reaction on a 1 mmol scale. In addition, decreasing the amount of the starting heteroarene to 1.05 equivalents did not diminish the yield of the biaryl product. This example illustrates the potential of this methodology to be used for large-scale applications.

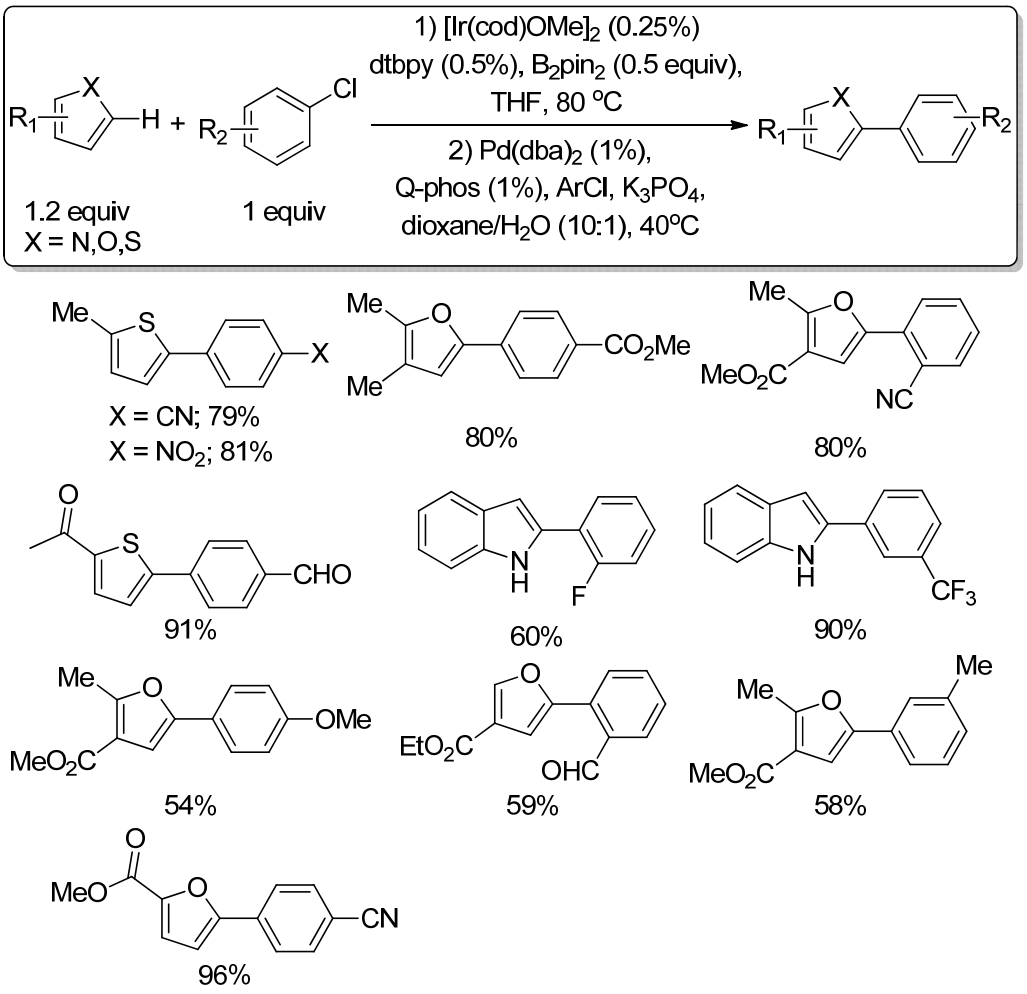


(4)

The coupling of 2-heteroaryl pinacol boronate esters with less reactive, but often more commercially available aryl chlorides, also occurs in good yield (Table 13). Because aryl chlorides are less reactive than aryl bromides, we conducted these reactions with a catalyst[2d] formed from the combination of 1 mol % $Pd(dba)_2$ and 1 mol % of the hindered alkylphosphine Q-phos (1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene), both of which are commercially available, with K_3PO_4 in a 10:1 mixture of 1,4-dioxane:H_2O at 40 °C. Similar to the borylation and coupling sequence with aryl bromides, this methodology tolerates a variety of functional groups, including cyano groups, nitro groups, alkoxycarbonyl, formyl, and trifluoromethyl groups.

Both electron-rich and electron-deficient aryl chlorides coupled with the intermediate pinacol boronate to give a good yield of product from the two-step, one-pot process.

Table 13. Scope of Ir-catalyzed borylation/Pd-catalyzed cross-coupling of heteroarenes with aryl chlorides



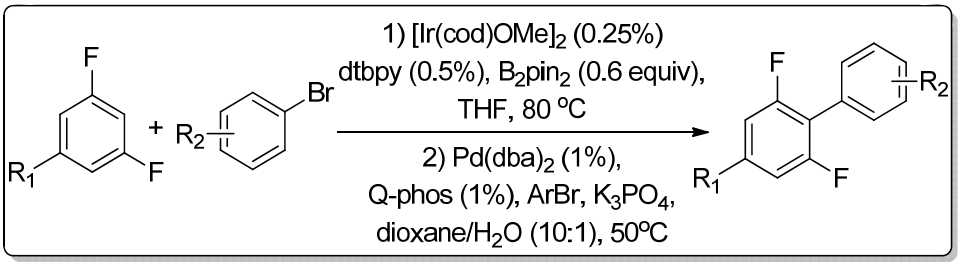
To create a process for the C-H borylation and coupling of fluoroarenes with aryl bromides, a more active catalyst for the coupling of the pinacol boronic esters than that containing P(*o*-tol)$_3$ was needed because of the susceptibility of the polyfluoroarenes to protodeborylation. The coupling of 2,3-difluoroaryl and 2,6-di-fluoroaryl pinacol boronate esters with aryl bromides occurred in the presence of 1 mol % of the Pd-Q-phos

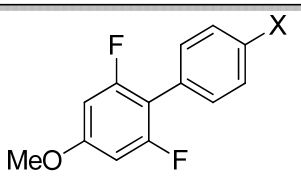
catalyst with K_3PO_4 as base in a 10:1 mixture of 1,4-dioxane:H_2O at 50 °C. As shown in Table 14, the two-step, one-pot procedure for borylation of a difluoroarene and Suzuki coupling occurred with a variety of aryl bromides, including electron-rich and electron-poor aryl bromides and *ortho*-substituted aryl bromides. Similar to the cross coupling with 2-heteroaryl pinacol boronates, this method tolerates a variety of functional groups having various electronic properties. In general, the coupling proceeded in higher yield with pinacolboronates containing an electron-donating substituent at the para position than with pinacolboronates containing an electron-withdrawing substituent at the para position.

Having demonstrated the synthetic utility of the one-pot borylation and Suzuki-Miyaura coupling of heteroarenes and difluoroarenes, we sought to determine the factors that enable the Suzuki-Miyaura coupling of the pinacol boronate esters to proceed in high yields. To determine the rate of decomposition of the pinacol boronate esters, relative to the rates of the coupling reaction, we treated a THF solution of three different 2-heteroaryl pinacol boronate esters with 2M aqueous Na_2CO_3 to mimic the aqueous basic conditions in the catalytic reaction and monitored the decomposition of the heteroaryl boronate at room temperature over time (Table 15). A majority of the 2-heteroaryl pinacol boronate esters derived from nitrogen, oxygen and sulfur heterocycles remained in solution after 5 h, the approximate time of the catalytic reaction. The amount of decomposition of the nitrogen and sulfur heteroaryl boronates was approximately the same as that of phenyl pinacol boronate ester, showing the degree of increased stability of these 2-heteroaryl pinacol boronates over boronic acids and other esters. Similar experiments performed with 2,6-difluorophenyl pinacol boronate esters showed that

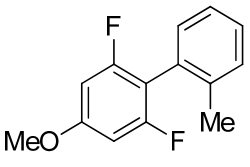
complete decomposition of these compounds occurred within 30 minutes at 50 °C. This greater lability explains the need to use a more active catalyst, such as the Pd-Q-phos catalyst, to achieve faster rates for the Suzuki-Miyaura coupling reaction with these boronates.

Table 14. Scope of Ir-catalyzed borylation/Pd-catalyzed cross coupling of polyfluorophenyl derivatives with aryl bromides

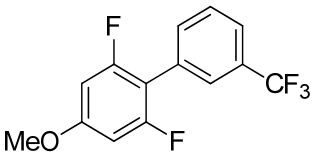




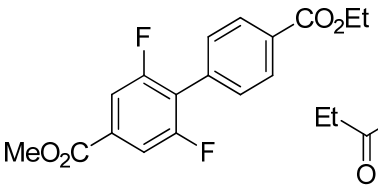
X = Me; 77%
X = OMe; 74%
X = NMe$_2$; 73%



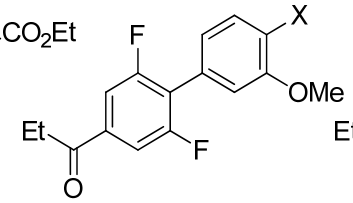
70%



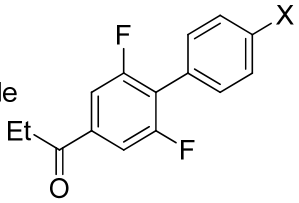
90%



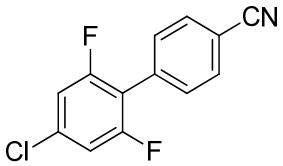
84%



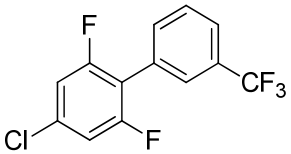
X = H; 72%
X = OMe; 61%



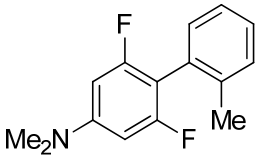
X = Cl; 66%
X = OPiv; 56%



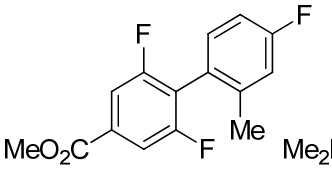
77%



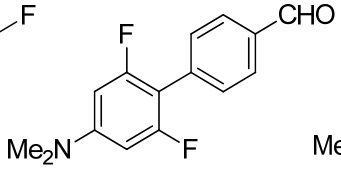
67%



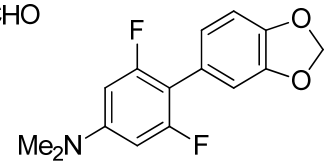
94%



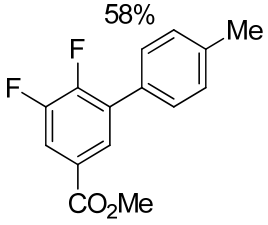
58%



71%

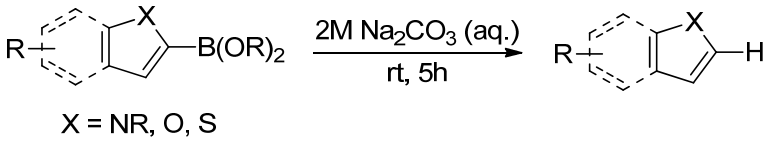


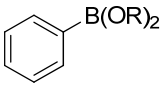
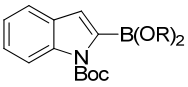
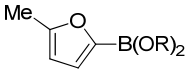
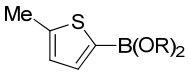
64%



88%

Table 15. Decomposition of heteroaryl pinacol boronate esters with aqueous base at room temperature



Entry	Aryl Boronate	%Ar-Bpin Remaining	% ArB(OH)$_2$ Remaining
1		87%	-
2		73%[a]	<2%
3		72%	9%
4		88%	74%

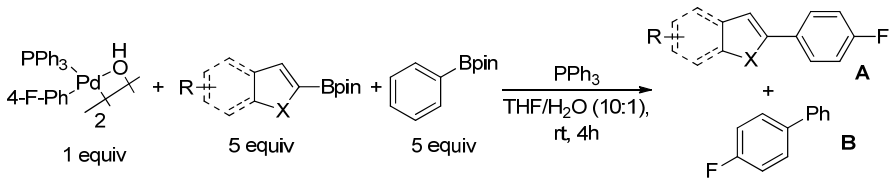
[a] The analogous reaction with the corresponding indolylboronic ester left 87% of the ArBpin unreacted

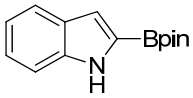
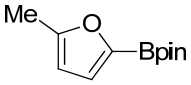
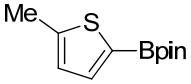
This greater stability of pinacolboronate esters is only beneficial if transmetallation, which is commonly proposed to be the turnover-limiting step in the Suzuki coupling reaction,[8a] of the esters is faster than the decomposition of the organoboron compound. The palladium hydroxo complex was shown recently to be the palladium species that reacts with the boron reagents in the transmetallation step.[8] Thus, to assess the relative rates of transmetallation of the heteroaryl and fluoroaryl boronic esters, we conducted a series of competition experiments involving the reaction of an arylpalladium(II) hydroxide complex with 5 equiv of a 2-heteroaryl pinacol boronate ester and 5 equiv of

phenyl pinacol boronate ester. These reactions formed, almost exclusively (>90%), the coupled product derived from the 2-heteroaryl pinacol boronate ester (Table 16); negligible amounts of product from coupling of the phenyl boronate ester (<5%) was observed. This result indicates that transmetallation of the 2-heteroaryl pinacol boronate esters is significantly faster than transmetallation of standard aryl pinacol boronate esters. This rapid transmetallation could result from hydrogen bonding between the heterocycle and the palladium intermediate or coordination of the electron-rich alkene of the heteroarenes to the palladium complex before transmetallation.

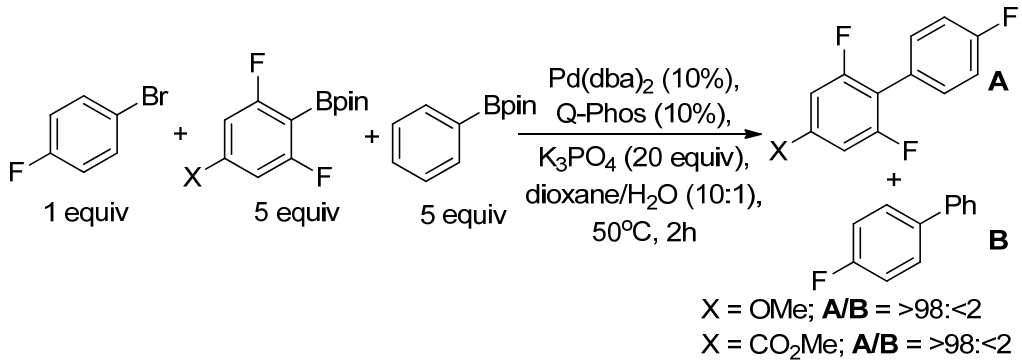
Similar competition experiments between 2,6-difluorophenyl pinacol boronates and the parent phenyl pinacol boronate ester showed that the 2,6-difluorophenylboronic ester reacts faster than the phenylboronic ester. The competition reaction yielded almost exclusively product from the 2,6-difluorophenyl pinacol boronate ester (Scheme 46).[15] These competition experiments, in combination with the data on the stability of the boronic esters, indicate that the high yields for coupling of 2-heteroaryl pinacol boronate esters and 2,6-difluoroaryl pinacol boronate esters result from the combination of their stability under aqueous basic conditions, and rapid transmetallation.

Table 16. Competition experiments between 2-heteroaryl and phenyl pinacol boronate esters



Entry	Heteroaryl Bpin	Yield of A	Yield of B
1		93%	5%
2		>98%	1%
3		>98%	1%

Scheme 46. Competition experiments between 2,6-difluoroaryl and phenyl pinacol boronate esters



4.4 Conclusion and Outlook

In summary, 2-heteroaryl and polyfluoroaryl pinacol boronate esters form in good yield by Ir-catalyzed C-H borylation, and Suzuki-Miyaura cross coupling of these boronates generated *in situ* occurs with simple palladium catalysts. Although useful as

formed *in situ*, the pinacol boronate esters are isolable and stable in air at room temperature, as opposed to the corresponding boronic acids, which require cold, anaerobic storage. Suzuki-Miyaura coupling of 2-heteroaryl and polyfluoroaryl pinacol boronates generated *in situ* also occurs with aryl halides with easily accessible catalysts. Because of its generality, this methodology should be useful for the preparation of heteroaryl and fluoroaryl compounds with diverse applications.

4.5 Experimental Information

General Procedures. All reactions were conducted under a nitrogen atmosphere in flame-dried glassware or in an inert atmosphere glovebox. Dry and degassed solvents were used unless otherwise noted. The water used as co-solvent was deionized and degassed by bubbling N_2 gas for 10 minutes. Column chromatography was performed with a Teledyne Isco Combiflash® R_f system with Redi*Sep* R_f columns. Analytical thin-layer chromatography was performed on glass plates coated with silica gel (Silicycle, 60 A pore size, 40-64 um particle size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by ultraviolet light and staining solution of *p*-anisaldehyde or KMnO4.

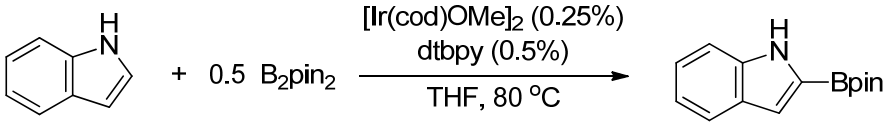
Materials. $[Ir(cod)OMe]_2$ and Q-phos (1,2,3,4,5-Pentaphenyl-1'-(di-*t*-butylphosphino)ferrocene) were obtained from Johnson Matthey and used as received. 4,4'-Di-*tert*-butylbipyridine was obtained from Aldrich Chemicals and used as received. Bis(pinacolato)diboron (B_2pin_2) was obtained from Allychem and used as received. Arenes, heteroarenes, aryl halides, tri-*o*-tolylphosphine, sodium carbonate, potassium phosphate, and pinacolborane were obtained from Aldrich, Alfa Aesar, Acros, Combiblocks, Oakwood Chemicals or TCI America and used as received. Heteroaryl boronic acids and boronate esters were obtained from Combi-Blocks or Aldrich and used as received. $Pd(dba)_2$ was synthesized according to published procedures.[16] Pd-hydroxide complexes were prepared according to published procedures.[8a,17]

Instruments. ^1H NMR spectra were recorded on a 500 MHz Varian instrument (126 MHz for ^{13}C). Chemical shifts are reported in parts per million relative to residual protiated solvent (7.26 ppm for $CDCl_3$). The carbon bonded to boron in the arene and

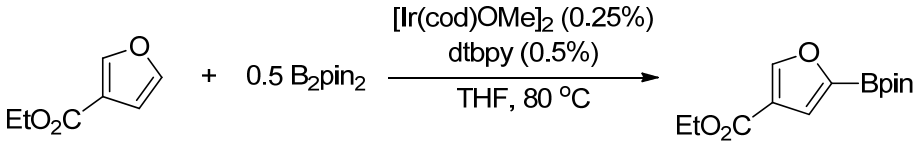
heteroarene borylation products were not observed via ^{13}C NMR spectroscopy. This is consistent with previous reports of borylated arenes and heteroarenes.[18] GC-MS data were obtained on an Agilient 6890-N GC system containing an Alltech EC-1 capillary column and an Agilient 5973 mass selective detector. GC analyses were obtained on an Agilent 6890 Gas Chromatograph equipped with an HP- 5 25 m x 0.20 mm ID x 0.33 μm capillary column (Agilent) and an FID detector.

Experimental Procedures

General Procedure for the Borylation of Heteroarenes. Inside a glove box, $[Ir(cod)OMe]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (127 mg, 0.500 mmol, 0.500 equiv) or HBpin (141 mg, 1.10 mmol, 1.10 equiv), the heteroarene (1.00 mmol, 1.00 equiv), and THF (2 mL) were added consecutively to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature, concentrated and purified by column chromatography to give the product.

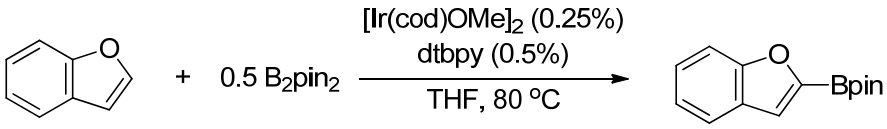


Borylation of Indole. Prepared according to the general procedure with indole (117 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (175 mg, 72%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.40 (m, 1H), 7.25 (m, 1H), 7.13 (m, 2H), 1.38 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.48, 128.55, 123.87, 121.85, 120.03, 114.12, 111.51, 84.40, 25.07. Anal. Calcd for $C_{14}H_{17}BNO_2$: C, 68.17; H, 7.46; N, 5.76. Found: C, 69.55; H, 7.42; N, 6.08.

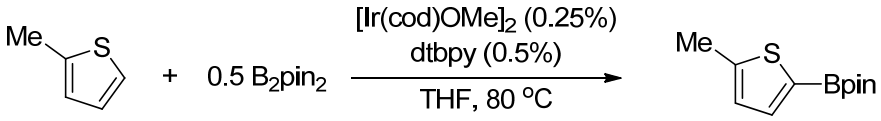


Borylation of ethyl 3-furoate. Prepared according to the general procedure with ethyl 3-furoate (140 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (172 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.31 (s, 1H), 4.22 (q, J = 6.9 Hz, 2H), 1.24 (m, 15H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.06, 151.99, 123.01, 120.45, 84.77, 60.65, 24.88, 14.43. Anal. Calcd for $C_{13}H_{19}BO_5$: C, 58.68; H, 7.20. Found: C, 58.75; H, 7.12.



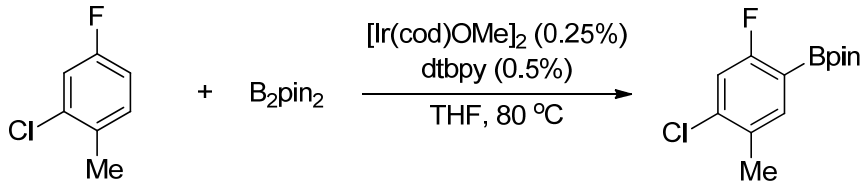
Borylation of Benzofuran. Prepared according to the general procedure with benzofuran (118 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (151 mg, 62%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.42 (s, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 1.39 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.77, 127.74, 126.18, 122.97, 122.13, 119.81, 112.18, 84.90, 25.01. Anal. Calcd for $C_{14}H_{17}BO_3$: C, 68.89; H, 7.02. Found: C, 68.86; H, 7.37.



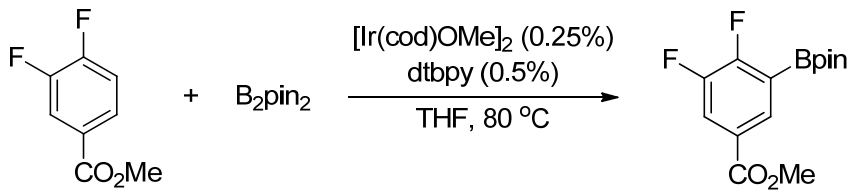
Borylation of 2-Methylthiophene. Prepared according to the general procedure with 2-methylthiophene (98 mg, 1.0 mmol, 1.0 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (166 mg, 74%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.48 (d, *J* = 3.4 Hz, 1H), 6.86 (d, *J* = 3.3 Hz, 1H), 2.55 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.73, 137.89, 127.24, 84.08, 24.99, 15.62. Anal. Calcd for $C_{11}H_{17}BO_2S$: C, 58.95; H, 7.65. Found: C, 58.71; H, 7.40.

General Procedure for the Borylation of Fluoroarenes. Inside a glove box, $[Ir(cod)OMe]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (153 mg, 0.600 mmol, 0.600 equiv) or HBpin (141 mg, 1.10 mmol, 1.10 equiv), the arene (1.00 mmol, 1.00 equiv), and THF (2 mL) were added

consecutively to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and purified by column chromatography to give the product.

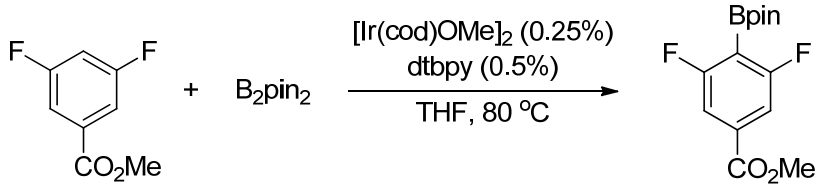


Borylation of 2-chloro-4-fluorotoluene. Prepared according to the general procedure with 2-chloro-4-fluorotoluene (144 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (223 mg, 83%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.58 (d, J = 6.3 Hz, 1H), 7.07 (d, J = 8.9 Hz, 1H), 2.33 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.46 (d, J = 252.9 Hz), 138.45 (d, J = 8.7 Hz), 131.57 (d, J = 3.7 Hz), 116.52 (d, J = 5.3 Hz), 116.30 (d, J = 5.1 Hz), 84.25 (s), 25.01 (s), 19.18 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.11 (s). Anal. Calcd for $C_{13}H_{17}BClFO_2$: C, 57.71; H, 6.33. Found: C, 58.04; H, 6.14.

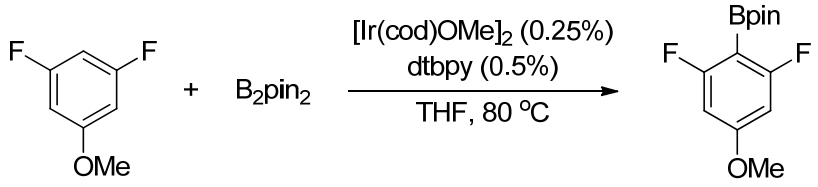


Borylation of Methyl 3,4-difluorobenzoate. Prepared according to the general procedure with methyl 3,4-difluorobenzoate (172 mg, 1.0 mmol, 1.0 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (217 mg, 73%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.16 (dd, J = 4.1, 2.0 Hz, 1H), 7.88 (ddd, J = 10.2, 7.6, 2.2 Hz, 1H), 3.90 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.40 (d, J = 2.3 Hz), 157.71 (dd, J = 260.6, 12.0 Hz), 150.25 (dd, J = 250.5,

14.9 Hz), 133.244 (dd, *J* = 7.9 Hz, 3.7 Hz), 126.83 (t, *J* = 4.4Hz), 121.491 (dd, *J* = 18.8 Hz, 2.3 Hz), 84.73 (s), 52.58 (s), 24.99 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.44 (dd, J = 4.1, 21.3), -137.78 (dd, J = 10.5, 21.2). Anal. Calcd for $C_{14}H_{17}BF_2O_4$: C, 56.41; H, 5.75. Found: C, 56.30; H, 5.68.



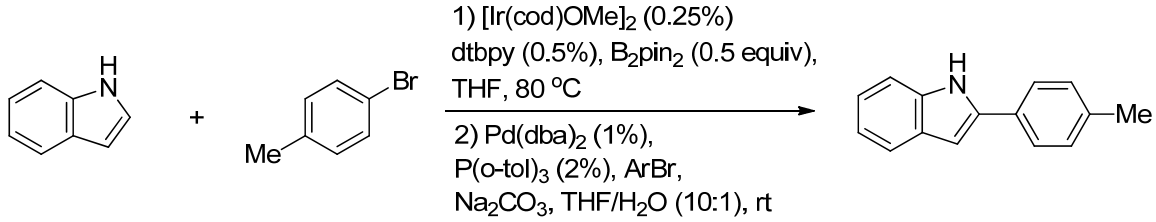
Borylation of Methyl 3,5-difluorobenzoate. Prepared according to the general procedure with methyl 3,5-difluorobenzoate (172 mg, 1.0 mmol, 1.0 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (202 mg, 68%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.48 (m, 2H), 3.91 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.36 (dd, *J* = 251.3, 12.8 Hz), 165.03 (t, *J* = 3.4 Hz), 135.25 (t, *J* = 9.9 Hz), 112.35 (m), 84.88 (s), 52.82 (s), 24.91 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.06 (d, J = 6.5). Anal. Calcd for $C_{14}H_{17}BF_2O_4$: C, 56.41; H, 5.75. Found: C, 56.15; H, 6.01.



Borylation of 3,5-difluoroanisole. Prepared according to the general procedure with 3,5-difluoroanisole (144 mg, 1.0 mmol, 1.0 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (200 mg, 74%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 6.38 (d, *J* = 9.5 Hz, 2H), 3.78 (s, 3H), 1.35 (s, 12H). ^{13}C

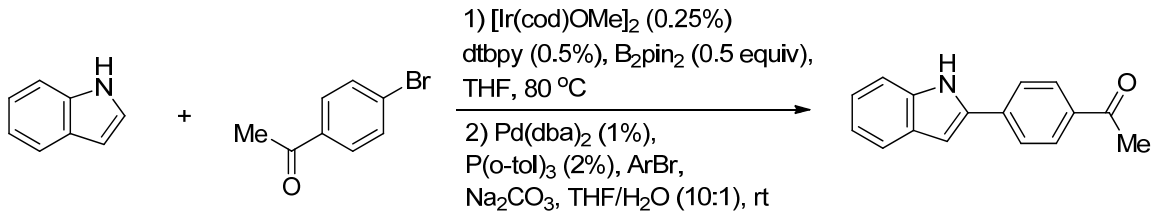
NMR (126 MHz, $CDCl_3$) δ 168.19 (dd, J = 249.8, 16.6 Hz), 164.11 (t, J = 14.7 Hz), 97.92 (m), 83.94 (s), 55.94 (s), 24.94 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.53 (d, J = 8.2). Anal. Calcd for $C_{13}H_{17}BF_2O_3$: C, 57.81; H, 6.34. Found: C, 57.82; H, 6.24.

General Procedure for one-pot C-H Borylation and Suzuki-Miyaura cross-coupling of heteroarenes with aryl bromides. Inside a glove box, $[Ir(cod)OMe]_2$ (2.0 mg, 0.0030 mmol, 0.0030 equiv), dtbpy (1.6 mg, 0.0060 mmol, 0.0060 equiv), B_2pin_2 (153 mg, 0.600 mmol, 0.600 equiv), the heteroarene (1.20 mmol, 1.20 equiv), and THF (2 mL) were added consecutively to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature, and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), tri-*o*-tolylphosphine (6.1 mg, 0.020 mmol, 0.02 equiv), Na_2CO_3 (424 mg, 4.00 mmol, 4.00 equiv), the aryl halide (1.00 mmol, 1.00 equiv), THF (3 mL) and degassed H_2O (0.3 mL) were added consecutively to the reaction mixture. The reaction mixture was sealed and stirred at room temperature for 18 h. The reaction mixture was filtered through silica gel, washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

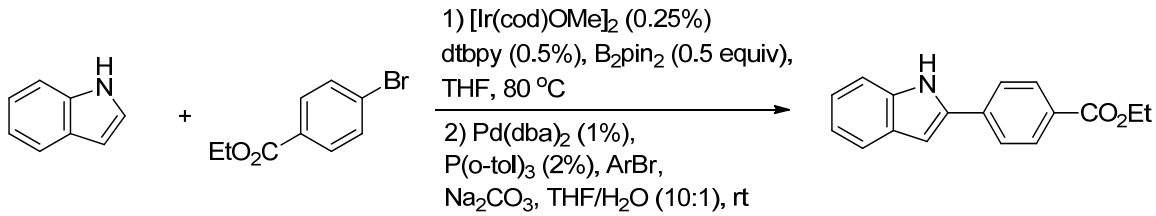


Arylation of indole with 4-bromotoluene. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10%

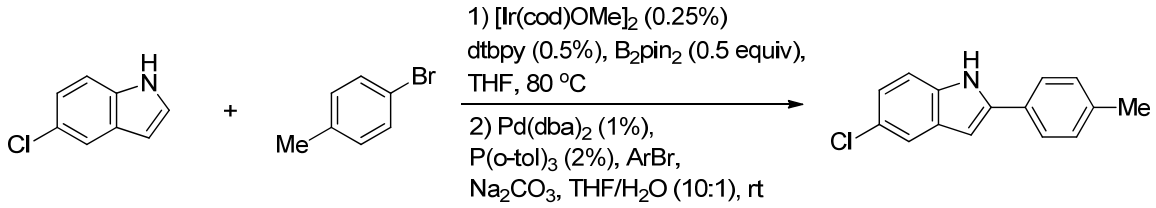
EtOAc:90% hexanes) to give the product (174 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.22 (m, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.82 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.32, 137.89, 136.95, 129.96, 128.69, 125.32, 122.37, 120.77, 120.45, 111.10, 102.85, 99.64, 21.51. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.60; H, 6.29; N, 6.79.



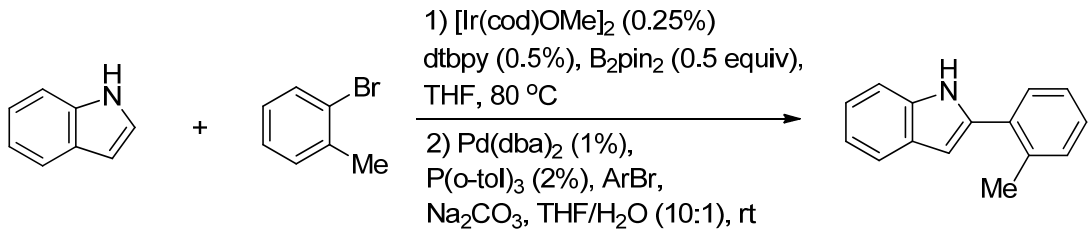
Arylation of indole with 4-bromoacetophenone. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 4-bromoacetophenone (199 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (129 mg, 55%). ^{1}H NMR (499 MHz, Acetone-d^6) δ 10.88 (s, 1H), 8.06 (m, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 2H), 2.60 (s, 4H). ^{13}C NMR (126 MHz, Acetone-d^6) δ 196.56, 138.19, 137.01, 136.84, 136.01, 129.21, 125.01, 122.86, 120.90, 120.16, 111.63, 101.37, 26.02. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.78; H, 5.59; N, 5.95.



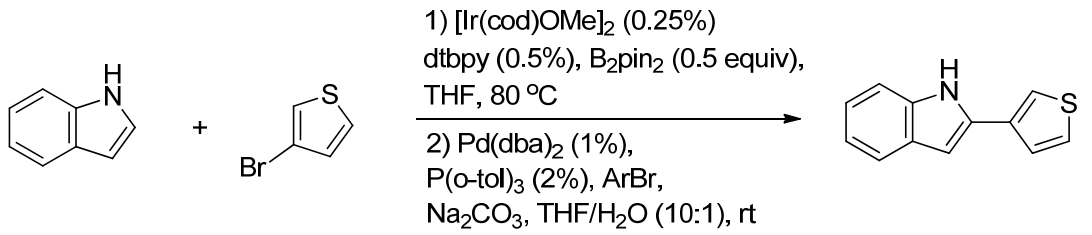
Arylation of indole with ethyl 4-bromobenzoate. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and ethyl 4-bromobenzoate (229 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (231 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 2.8 Hz, 1H), 6.92 (s, 1H), 6.58 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.94, 157.04, 146.34, 135.95, 128.26, 125.55, 122.36, 121.38, 119.07, 116.88, 111.76, 103.27, 102.79, 60.79, 14.61. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.48; H, 5.21; N, 5.47. C, 76.10; H, 5.46; N, 5.29.



Arylation of 5-chloroindole with 4-bromotoluene. Prepared according to the general procedure with 5-chloroindole (182 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (189 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.26 (m, 2H), 7.12 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.72 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.68, 138.36, 135.20, 130.61, 130.01, 129.25, 125.97, 125.35, 122.53, 120.05, 111.97, 99.19, 21.52. Anal. Calcd for $C_{15}H_{12}ClN$: C, 74.53; H, 5.00; N, 5.79. Found: C, 74.22; H, 4.78; N, 5.74.

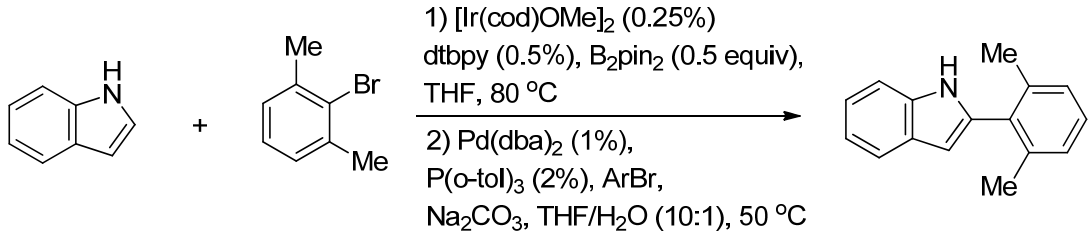


Arylation of indole with 2-bromotoluene. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 2-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (151 mg, 73%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.54 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.41 (m, 2H), 7.34 (m, 1H), 7.29 (m, 1H), 6.74 (s, 1H), 2.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.79, 136.51, 136.42, 132.96, 131.40, 129.34, 129.20, 128.30, 126.41, 122.39, 120.88, 120.40, 111.16, 103.29, 21.43. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.76; H, 6.16; N, 6.76.

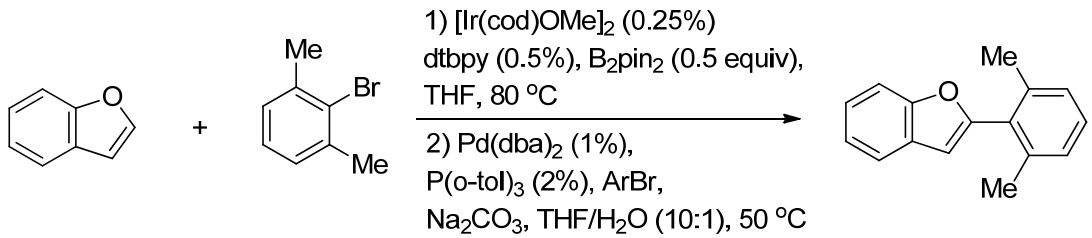


Arylation of indole with 3-bromothiophene. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 3-bromothiophene (163 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (148 mg, 74%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.63 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.43 (s, 3H), 7.39 (m, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.73 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.65, 134.37, 134.18, 129.33, 126.88, 125.94, 122.51,

120.81, 120.51, 119.31, 110.97, 100.21. Anal. Calcd for $C_{12}H_9NS$: C, 72.33; H, 4.55; N, 7.03. Found: C, 72.39; H, 4.56; N, 7.03.

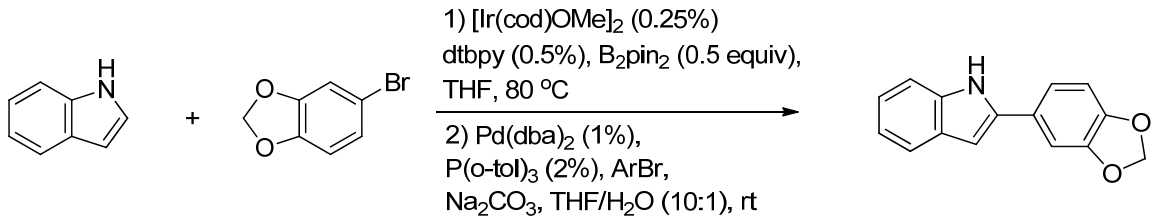


Arylation of indole with 2,6-dimethylbromobenzene. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 2,6-dimethylbromobenzene (185 mg, 1.00 mmol, 1.00 equiv) and the Suzuki coupling step at 50 °C. The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (159 mg, 72%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.43 (m, 1H), 7.27 (m, 3H), 7.20 (m, 2H), 6.46 (s, 1H), 2.24 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.64, 136.44, 136.18, 133.32, 129.06, 128.77, 127.62, 121.78, 120.67, 120.06, 110.98, 102.78, 20.87. Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.59; H, 6.76; N, 6.09.

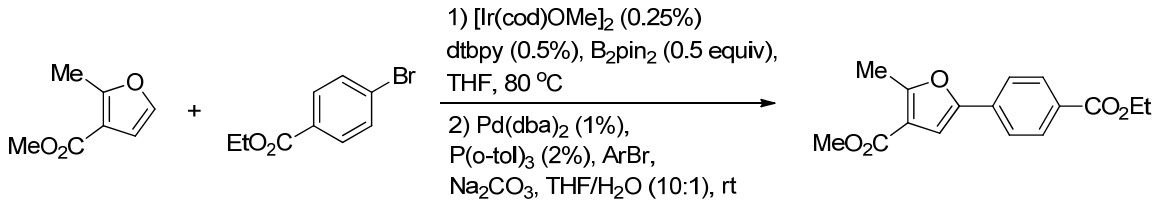


Arylation of benzofuran with 2,6-dimethylbromobenzene. Prepared according to the general procedure with benzofuran (142 mg, 1.20 mmol, 1.20 equiv) and 2,6-dimethylbromobenzene (185 mg, 1.00 mmol, 1.00 equiv) and the Suzuki coupling step at 50 °C. The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (159 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (m, 1H),

7.61 (m, 1H), 7.36 (m, 3H), 7.23 (m, 2H), 6.75 (s, 1H), 2.36 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.14, 155.06, 138.84, 130.91, 129.48, 129.08, 127.88, 124.11, 122.97, 121.09, 111.51, 106.42, 20.93. Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.41; H, 6.17.

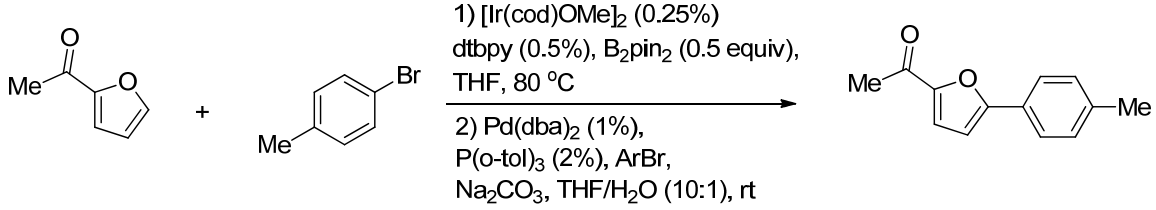


Arylation of indole with 1-Bromo-3,4-(methylenedioxy)benzene. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 1-Bromo-3,4-(methylenedioxy)benzene (201 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (199 mg, 84%). ^{1}H NMR (499 MHz, Acetone-d6) δ 9.74 (s, 1H), 6.76 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.59 (m, 3H), 6.30 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.23 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.15 (d, *J* = 8.5 Hz, 1H), 6.01 (m, 1H), 5.27 (s, 2H). ^{13}C NMR (126 MHz, Acetone) δ 148.63, 147.50, 138.21, 137.55, 129.63, 127.33, 121.69, 120.20, 119.75, 118.99, 111.18, 108.78, 105.84, 101.59, 98.61. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.68; H, 4.37; N, 5.63.

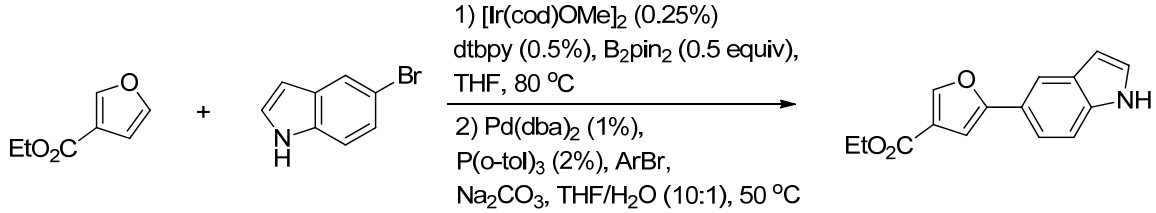


Arylation of methyl 2-methyl-3-furancarboxylate with ethyl 4-bromobenzoate. Prepared according to the general procedure with methyl 2-methyl-3-furancarboxylate

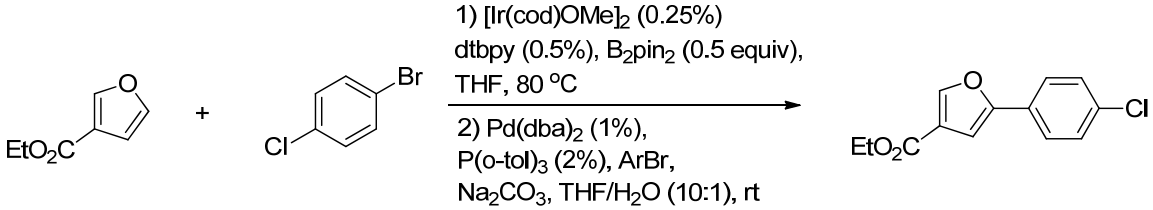
(168 mg, 1.20 mmol, 1.20 equiv) and ethyl 4-bromobenzoate (229 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (280 mg, 97%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.97 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 6.91 (s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.59 (s, 3H), 1.35 (t, J = 7.5 Hz 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.26, 164.20, 159.80, 150.84, 133.91, 130.20, 129.31, 123.30, 115.64, 107.77, 61.15, 51.60, 14.52, 14.05. Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.28; H, 5.50.



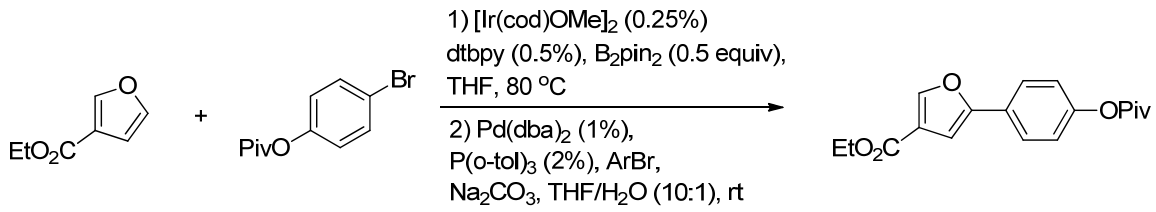
Arylation of 2-acetylfuran with 4-bromotoluene. Prepared according to the general procedure with 2-acetylfuran (132 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (138 mg, 69%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.75 (d, J = 3.4 Hz, 1H), 7.27 (m, 4H), 6.67 (d, J = 3.7 Hz, 1H), 2.54 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.74, 157.76, 151.93, 135.90, 131.69, 129.31, 128.16, 126.43, 111.02, 26.23, 22.02. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.97; H, 5.92.



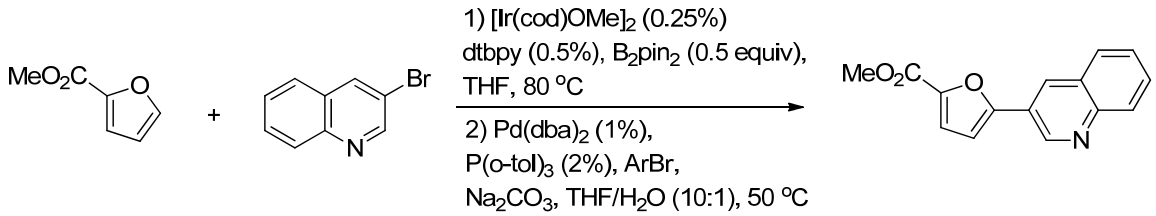
Arylation of ethyl 3-furoate with 5-bromoindole. Prepared according to the general procedure with ethyl 3-furoate (168 mg, 1.20 mmol, 1.20 equiv) and 5-bromoindole (196 mg, 1.00 mmol, 1.00 equiv) and the Suzuki coupling step at 50 °C. The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (225 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.04 (s, 1H), 7.52 (m, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.21 (t, J = 2.8 Hz, 1H), 6.93 (s, 1H), 6.59 (d, J = 3.0 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.94, 157.04, 146.34, 135.95, 128.26, 125.55, 122.36, 121.38, 119.07, 116.88, 111.76, 103.27, 102.79, 60.79, 14.61. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.40; H, 5.13; N, 5.42.



Arylation of ethyl 3-furoate with 4-bromochlorobenzene. Prepared according to the general procedure with ethyl 3-furoate (168 mg, 1.20 mmol, 1.20 equiv) and 4-bromochlorobenzene (192 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (223 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 0.8 Hz, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 6.95 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.15, 154.24, 147.10, 134.12, 129.24, 128.55, 125.46, 121.65, 105.18, 60.85, 14.56. Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42. Found: C, 61.94; H, 4.25.

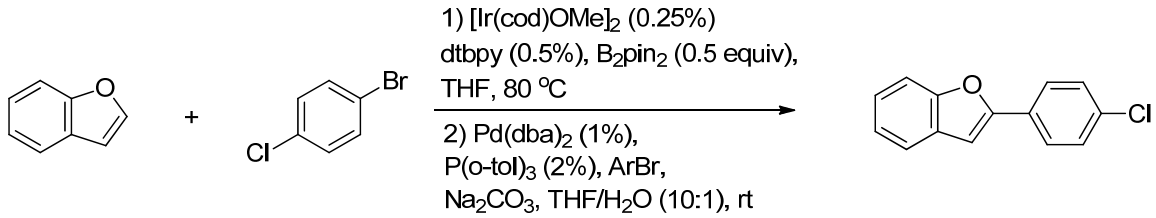


Arylation of ethyl 3-furoate with 4-bromophenyl pivalate. Prepared according to the general procedure with ethyl 3-furoate (168 mg, 1.20 mmol, 1.20 equiv) and 4-bromophenyl pivalate (257 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (253 mg, 80%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.94 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.37 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.10, 163.24, 154.68, 151.14, 146.95, 127.65, 125.31, 122.21, 121.58, 104.71, 60.77, 39.33, 27.34, 14.57. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 67.96; H, 6.41.

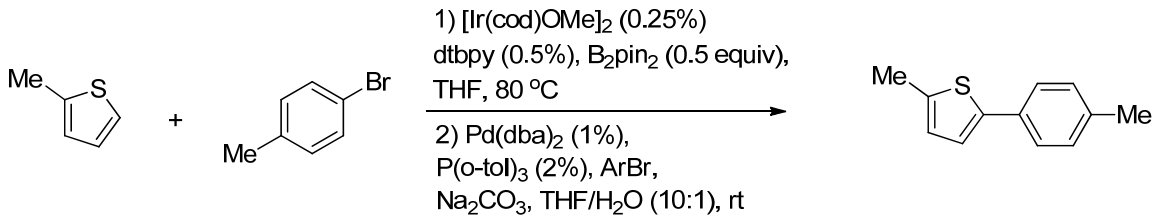


Arylation of methyl 2-furoate with 3-bromoquinoline. Prepared according to the general procedure with methyl 2-furoate (151 mg, 1.20 mmol, 1.20 equiv) and 3-bromoquinoline (208 mg, 1.00 mmol, 1.00 equiv) and the Suzuki coupling step at 50 °C. The mixture was purified by flash column chromatography (20% EtOAc:80% hexanes) to give the product (243 mg, 96%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 9.12 (d, J = 2.3 Hz, 1H), 8.40 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.62 (m, 1H), 7.48 (m, 1H), 7.20 (d, J = 3.6 Hz, 1H), 6.84 (d, J = 3.6 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.13, 154.91, 147.72, 147.05, 144.61, 131.17, 130.30,

129.38, 128.41, 127.69, 127.66, 122.80, 120.13, 108.48, 52.21. Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.18; H, 4.32; N, 5.45.

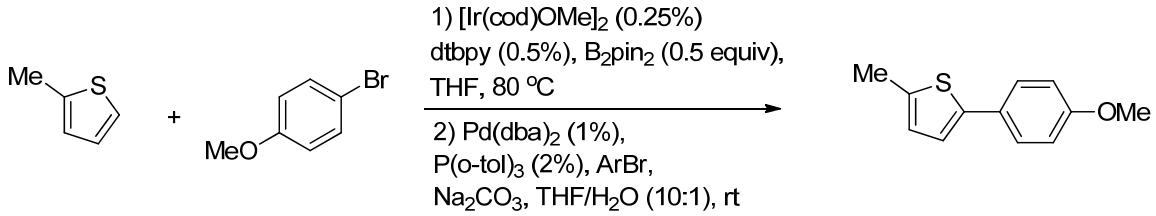


Arylation of benzofuran with 4-bromochlorobenzene. Prepared according to the general procedure with benzofuran (142 mg, 1.20 mmol, 1.20 equiv) and 4-bromochlorobenzene (192 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (194 mg, 85%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.61 (s, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 7.30 (m, 1H), 7.00 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.16, 155.01, 134.56, 129.35, 129.28, 129.21, 126.37, 124.85, 123.39, 121.31, 111.49, 102.04. Anal. Calcd for $C_{14}H_9ClO$: C, 73.53; H, 3.97. Found: C, 73.72; H, 3.91.

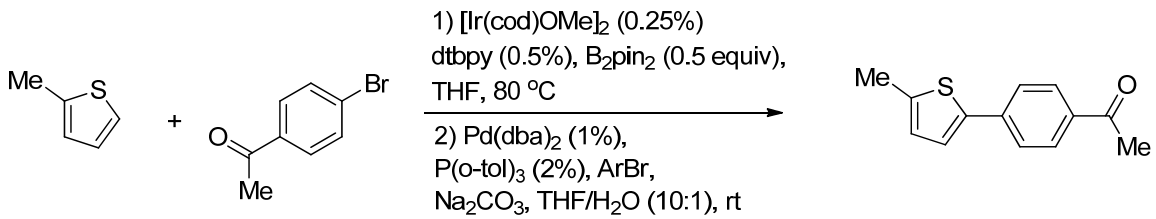


Arylation of 2-methylthiophene with 4-bromotoluene. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (171 mg, 91%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.17 (d,

J = 3.5 Hz, 1H), 6.82 (s, 1H), 2.60 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.50, 139.18, 137.08, 132.33, 129.81, 126.43, 125.75, 122.68, 21.46, 15.73. Anal. Calcd for $C_{12}H_{12}S$: C, 76.55; H, 6.42. Found: C, 76.37; H, 6.47.

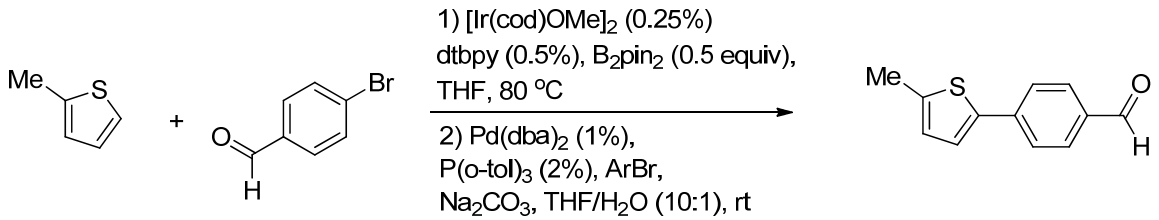


Arylation of 2-methylthiophene with 4-bromoanisole. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 4-bromoanisole (187 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (172 mg, 84%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.54 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 3.5 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 6.76 (m, 1H), 3.86 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.15, 142.20, 138.69, 127.95, 127.03, 126.35, 122.11, 114.51, 55.57, 15.67. Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92. Found: C, 70.36; H, 6.00.

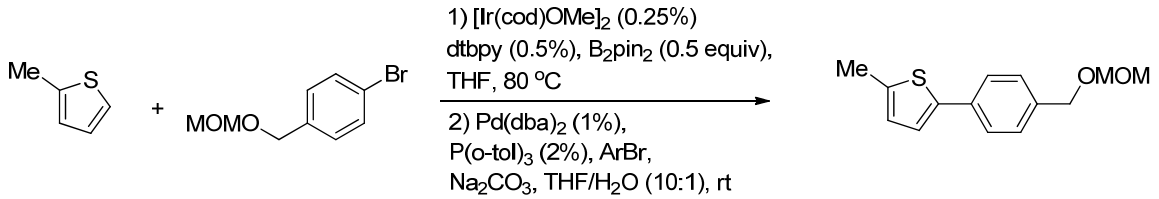


Arylation of 2-methylthiophene with 4-bromoacetophenone. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 4-bromoacetophenone (199 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (195 mg, 90%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.21 (d,

J = 3.6 Hz, 1H), 6.75 (d, J = 4.6 Hz, 1H), 2.58 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.48, 141.73, 140.67, 139.28, 135.46, 129.31, 126.94, 125.25, 124.86, 26.75, 15.79. Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59. Found: C, 72.50; H, 5.70.

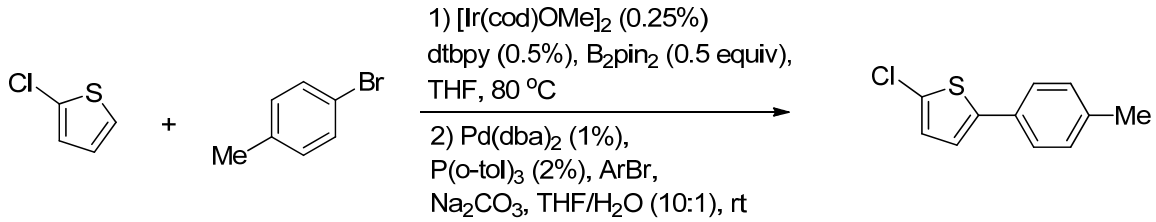


Arylation of 2-methylthiophene with 4-bromobenzaldehyde. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 4-bromobenzaldehyde (185 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (188 mg, 93%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 3.6 Hz, 1H), 6.76 (s, 1H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.65, 142.30, 140.59, 140.44, 134.86, 130.66, 127.09, 125.61, 125.35, 15.82. Anal. Calcd for $C_{12}H_{10}OS$: C, 71.25; H, 4.98. Found: C, 71.28; H, 4.86.

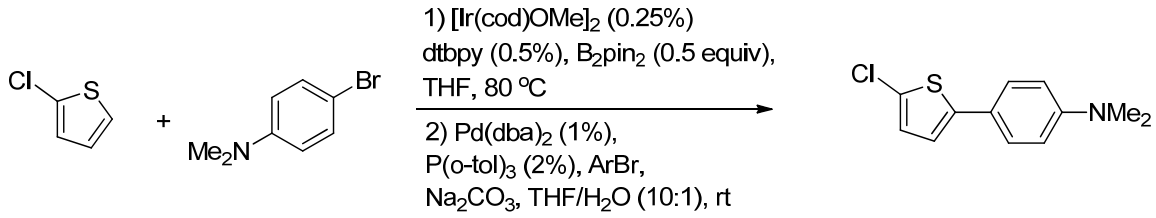


Arylation of 2-methylthiophene with 1-bromo-4-(methoxymethoxy)benzene. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 1-bromo-4-(methoxymethoxy)benzene (217 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (197 mg, 84%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H),

7.39 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 3.5 Hz, 1H), 6.77 (d, J = 3.5, 1H), 4.77 (s, 2H), 4.64 (s, 2H), 3.47 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.95, 139.76, 136.91, 134.45, 128.69, 126.51, 125.75, 123.22, 95.92, 69.11, 55.62, 15.72. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 68.01; H, 6.53.

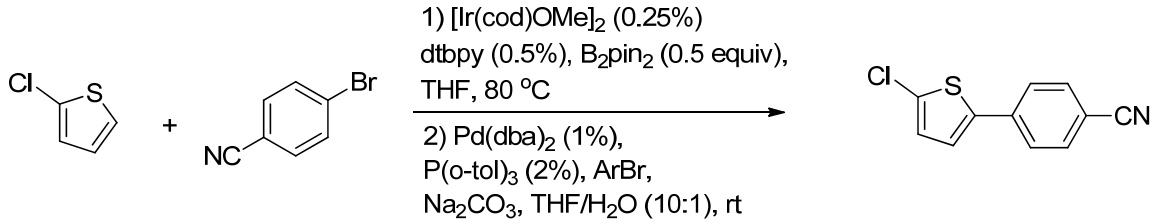


Arylation of 2-chlorothiophene with 4-bromotoluene. Prepared according to the general procedure with 2-chlorothiophene (143 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (192 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 3.9 Hz, 1H), 6.91 (d, J = 3.8 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.41, 138.04, 131.20, 129.95, 128.76, 127.31, 125.71, 121.96, 21.48. Anal. Calcd for $C_{11}H_9ClS$: C, 63.30; H, 4.35. Found: C, 63.35; H, 4.44.

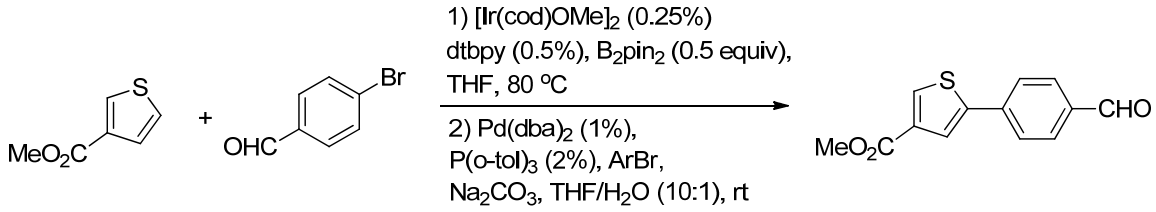


Arylation of 2-chlorothiophene with 4-bromo-*N*,*N*-dimethylaniline. Prepared according to the general procedure with 2-chlorothiophene (143 mg, 1.20 mmol, 1.20 equiv) and 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the

product (185 mg, 78%). ^{1}H NMR (499 MHz, Acetone) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 3.8 Hz, 1H), 6.96 (d, *J* = 3.9 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 2.99 (s, 6H). ^{13}C NMR (126 MHz, Acetone) δ 150.77, 129.19, 128.61, 127.70, 126.45, 121.66, 120.22, 112.66, 39.72. Anal. Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89. Found: C, 60.68; H, 4.96; N, 5.76.

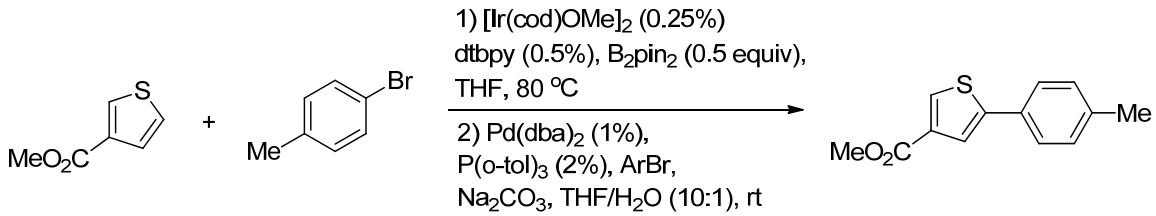


Arylation of 2-chlorothiophene with 4-bromobenzonitrile. Prepared according to the general procedure with 2-chlorothiophene (143 mg, 1.20 mmol, 1.20 equiv) and 4-bromobenzonitrile (182 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (187 mg, 85%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.56 (m, 2H), 7.18 (d, *J* = 3.9 Hz, 1H), 6.93 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.65, 137.95, 133.05, 131.97, 127.94, 125.84, 124.68, 118.89, 111.14. Anal. Calcd for $C_{11}H_6ClNS$: C, 60.14; H, 2.75; N, 6.38. Found: C, 59.97; H, 2.64; N, 6.14.

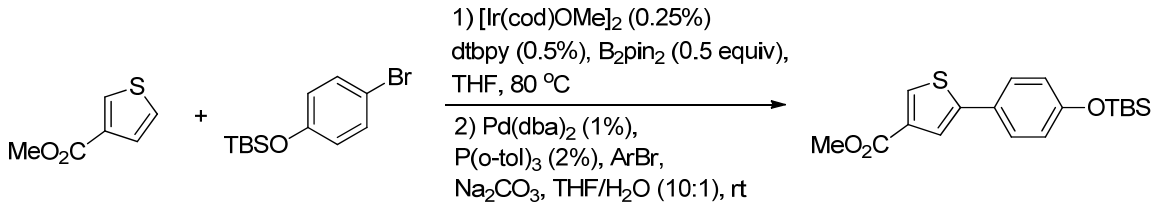


Arylation of methyl thiophene-3-carboxylate with 4-bromobenzaldehyde. Prepared according to the general procedure with methyl thiophene-3-carboxylate (171 mg, 1.20 mmol, 1.20 equiv) and 4-bromobenzaldehyde (185 mg, 1.00 mmol, 1.00 equiv). The

mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (204 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.04 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.76 (s, 1H), 7.67 (d, J = 8.2 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.49, 162.96, 143.41, 139.11, 135.74, 134.75, 133.46, 130.67, 126.20, 125.44, 52.22. Anal. Calcd for $C_{13}H_{10}O_3S$: C, 63.40; H, 4.09. Found: C, 63.11; H, 3.98.

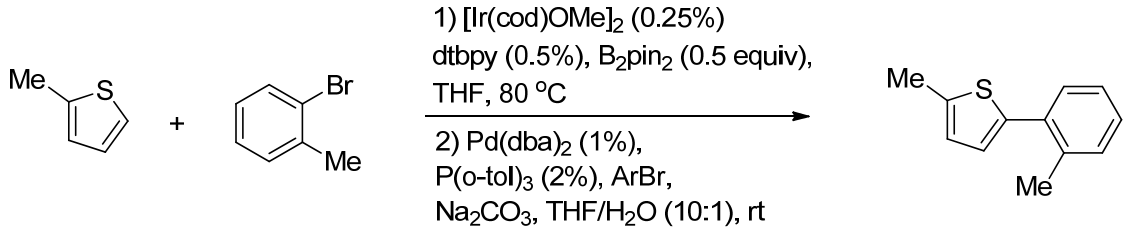


Arylation of methyl thiophene-3-carboxylate with 4-bromotoluene. Prepared according to the general procedure with methyl thiophene-3-carboxylate (171 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (221 mg, 95%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.69 (s, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 3.90 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.41, 145.46, 138.30, 134.34, 131.46, 130.96, 129.91, 126.03, 123.03, 52.03, 21.42. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.53; H, 5.23.

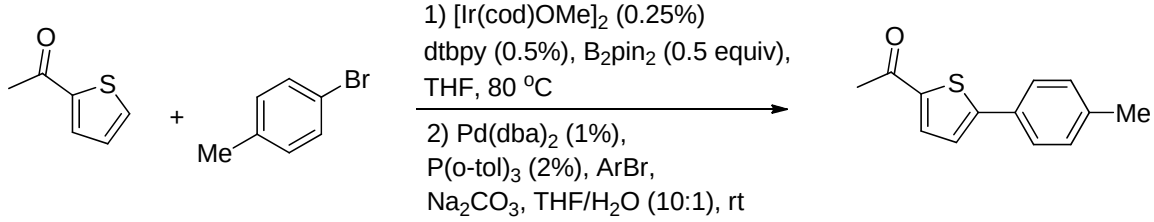


Arylation of methyl thiophene-3-carboxylate with (4-bromophenoxy)(tert-butyl)dimethylsilane. Prepared according to the general procedure with methyl

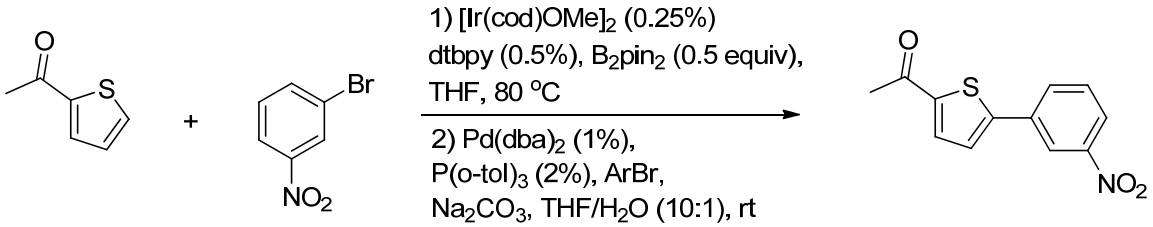
thiophene-3-carboxylate (171 mg, 1.20 mmol, 1.20 equiv) and (4-bromophenoxy)(tert-butyl)dimethylsilane (288 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (335 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 1.3 Hz, 1H), 7.59 (d, J = 1.3 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.86 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.40, 156.10, 145.25, 134.27, 131.10, 127.36, 127.09, 122.53, 120.80, 52.00, 25.91, 18.47, -4.16. Anal. Calcd for $C_{18}H_{24}O_3SSi$: C, 62.03; H, 6.94. Found: C, 61.97; H, 6.78.



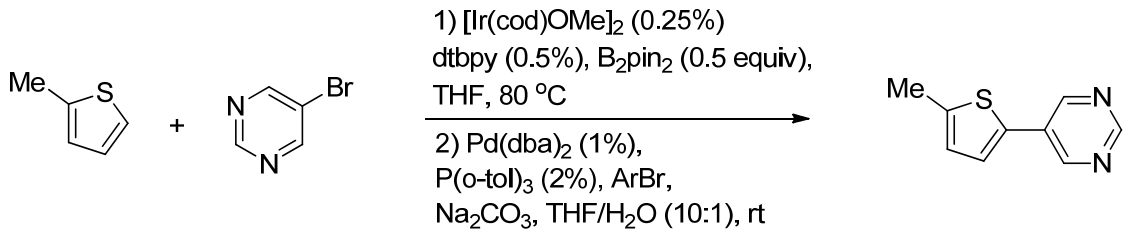
Arylation of 2-methylthiophene with 2-bromotoluene. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 2-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (181 mg, 96%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.33 (m, 3H), 6.97 (d, J = 3.4 Hz, 1H), 6.85 (d, J = 3.3 Hz, 1H), 2.63 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.18, 139.91, 136.21, 134.86, 131.06, 130.60, 127.80, 126.60, 126.21, 125.64, 21.57, 15.58. Anal. Calcd for $C_{12}H_{12}S$: C, 76.55; H, 6.42. Found: C, 76.87; H, 6.43.



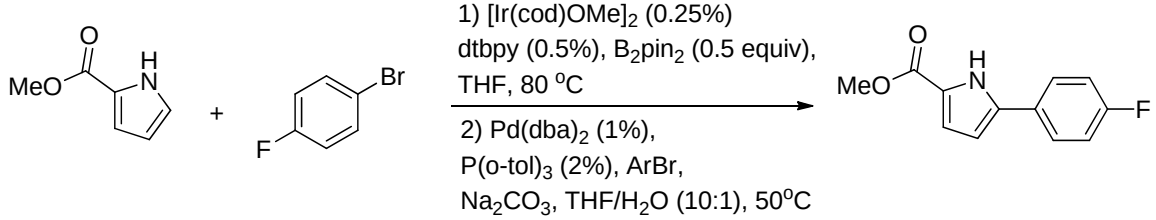
Arylation of 2-acetylthiophene with 4-bromotoluene. Prepared according to the general procedure with 2-acetylthiophene (152 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (195 mg, 90%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.61 (d, *J* = 4.0 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 3.9 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.66, 153.22, 142.78, 139.43, 133.79, 130.79, 130.02, 126.34, 123.63, 26.70, 21.51. Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59. Found: C, 72.52; H, 5.56.



Arylation of 2-acetylthiophene with 3-bromonitrobenzene. Prepared according to the general procedure with 2-acetylthiophene (152 mg, 1.20 mmol, 1.20 equiv) and 3-bromonitrobenzene (202 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (205 mg, 83%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.16 (m, 1H), 7.92 (m, 1H), 7.68 (d, *J* = 3.9 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 3.9 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.81, 149.33, 148.91, 144.83, 135.17, 133.67, 132.12, 130.48, 125.75, 123.53, 121.00, 25.04. Anal. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.66. Found: C, 58.37; H, 3.83; N, 5.43.

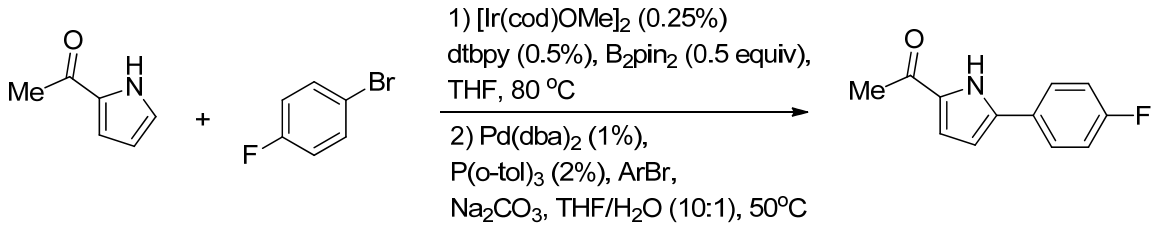


Arylation of 2-methylthiophene with 5-bromopyrimidine. Prepared according to the general procedure with 2-methylthiophene (118 mg, 1.20 mmol, 1.20 equiv) and 5-bromopyrimidine (159 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (139 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.83 (d, J = 2.2 Hz, 2H), 7.17 (t, J = 2.7 Hz, 1H), 6.76 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.95, 153.11, 142.56, 133.91, 129.05, 127.03, 125.42, 15.69. Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.24; H, 4.55; N, 15.56.

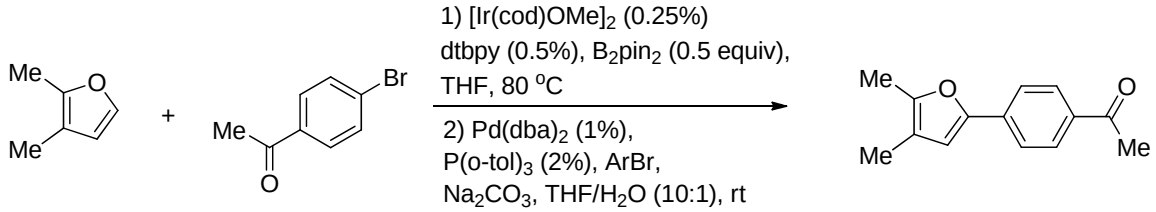


Arylation of methyl pyrrole-2-carboxylate with 4-fluorobromobenzene. Prepared according to the general procedure with methyl pyrrole-2-carboxylate (150 mg, 1.20 mmol, 1.20 equiv) and 4-fluorobromobenzene (175 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (199 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.59 (dd, J = 8.8, 5.2 Hz, 2H), 7.09 (t, J = 8.6 Hz, 2H), 6.96 (dd, J = 3.8, 2.4 Hz, 1H), 6.48 (dd, J = 3.8, 2.7 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.58 (d, J = 248.5 Hz), 162.14 (s), 136.56 (s), 128.01 (d, J = 3.3 Hz), 126.96 (d, J = 8.0 Hz), 123.25 (s), 117.26

(s), 116.16 (d, J = 21.8 Hz), 108.17 (s), 51.88 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.20 (s). Anal. Calcd for $C_{12}H_{10}FNO_2$: C, 65.75; H, 4.60; N, 6.39. Found: C, 65.49; H, 4.40; N, 6.17.



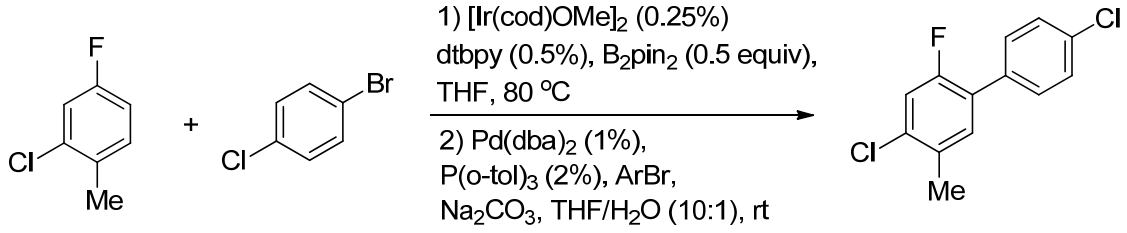
Arylation of 2-acetylpyrrole with 4-fluorobromobenzene. Prepared according to the general procedure with 2-acetylpyrrole (131 mg, 1.20 mmol, 1.20 equiv) and 4-fluorobromobenzene (175 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (152 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.69 (d, J = 5.4 Hz, 2H), 7.10 (m, 2H), 6.97 (d, J = 2.5 Hz, 1H), 6.50 (m, 1H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.10 (s), 162.81 (d, J = 248.2 Hz), 138.33 (s), 132.94 (s), 127.40 (d, J = 8.1 Hz), 119.05 (s), 116.12 (d, J = 21.9 Hz), 110.82 (s), 108.41 (s), 25.56 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.57 (s). Anal. Calcd for $C_{12}H_{10}FNO$: C, 70.93; H, 4.96; N, 6.89. Found: C, 70.58; H, 4.87; N, 6.83.



Arylation of 2,3-dimethylfuran with 4-bromoacetophenone. Prepared according to the general procedure with 2,3-dimethylfuran (116 mg, 1.20 mmol, 1.20 equiv) and 4-bromoacetophenone (199 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash

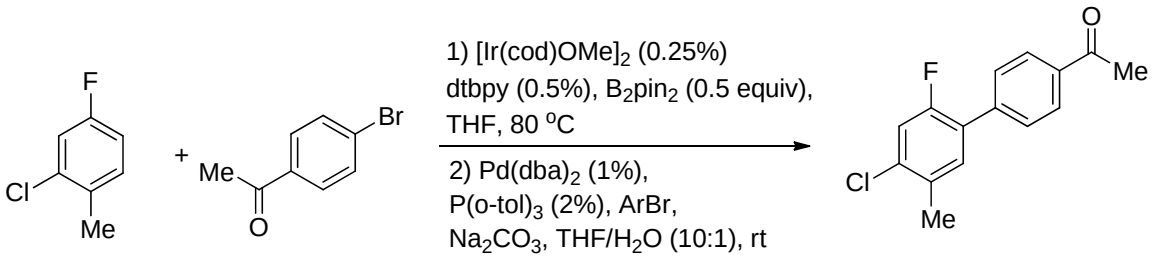
column chromatography (10% EtOAc:90% hexanes) to give the product (204 mg, 95%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 6.56 (s, 1H), 2.55 (s, 3H), 2.26 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.62, 149.95, 149.28, 135.46, 134.95, 129.14, 122.96, 117.10, 111.37, 26.62, 11.79, 10.09. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.48; H, 6.63.

General Procedure for one-pot C-H Borylation and Suzuki-Miyaura cross-coupling of *ortho*-fluoroarenes with aryl bromides. Inside a glove box, $[Ir(cod)OMe]_2$ (2.0 mg, 0.0030 mmol, 0.0030 equiv), dtbpy (1.6 mg, 0.0060 mmol, 0.0060 equiv), B_2pin_2 (183 mg, 0.720 mmol, 0.720 equiv), the heteroarene (1.20 mmol, 1.20 equiv), and THF (2 mL) were added consecutively to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature, and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), tri-*o*-tolylphosphine (6.1 mg, 0.020 mmol, 0.02 equiv), Na_2CO_3 (424 mg, 4.00 mmol, 4.00 equiv), the aryl halide (1.00 mmol, 1.00 equiv), THF (3 mL) and degassed H_2O (0.3 mL) were added consecutively to the reaction mixture. The reaction mixture was sealed and stirred at room temperature for 18 h. The reaction mixture was filtered through silica gel, washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

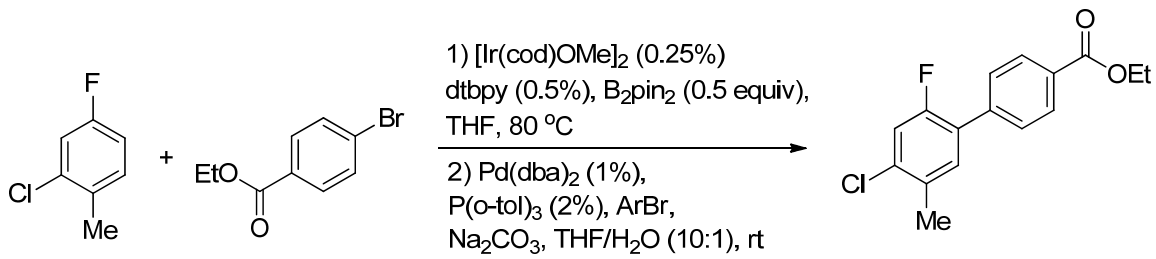


Arylation of 2-chloro-4-fluorotoluene with 4-chlorobromobenzene. Prepared according to the general procedure with 2-chloro-4-fluorotoluene (174 mg, 1.20 mmol,

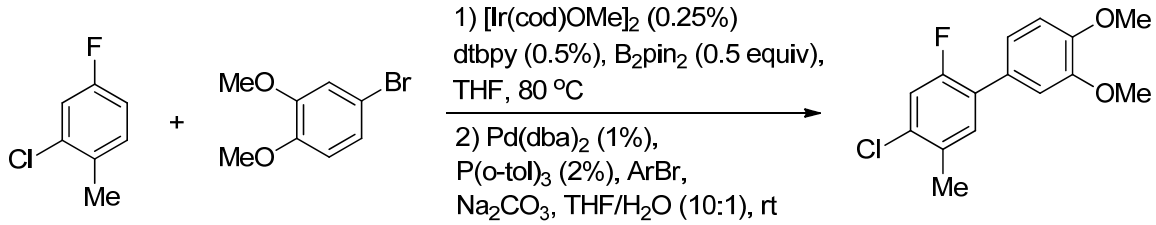
1.20 equiv) and 4-chlorobromobenzene (192 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (245 mg, 96%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.44 (m, 4H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 10.1 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.77 (d, *J* = 249.2 Hz), 134.22, 134.16, 133.59 (d, *J* = 1.7 Hz), 132.48 (d, *J* = 3.9 Hz), 132.17 (d, *J* = 3.8 Hz), 130.35 (d, *J* = 3.0 Hz), 128.97, 126.50 (d, *J* = 13.2 Hz), 117.22 (d, *J* = 26.2 Hz), 19.57. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.64. Anal. Calcd for $C_{13}H_9Cl_2F$: C, 61.20; H, 3.56. Found: C, 61.01; H, 3.54.



Arylation of 2-chloro-4-fluorotoluene with 4-bromoacetophenone. Prepared according to the general procedure with 2-chloro-4-fluorotoluene (174 mg, 1.20 mmol, 1.20 equiv) and 4-bromoacetophenone (199 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (222 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 10.1 Hz, 1H), 2.60 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.74, 157.80 (d, *J* = 249.9 Hz), 139.79 (d, *J* = 1.7 Hz), 136.40, 134.76 (d, *J* = 10.2 Hz), 132.58 (d, *J* = 3.8 Hz), 132.22 (d, *J* = 3.6 Hz), 129.20 (d, *J* = 3.2 Hz), 128.72 , 126.45 (d, *J* = 13.1 Hz), 117.26 (d, *J* = 26.1 Hz), 26.85, 19.53. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.24. Anal. Calcd for $C_{15}H_{12}ClFO$: C, 68.58; H, 4.60. Found: C, 68.61; H, 4.79.

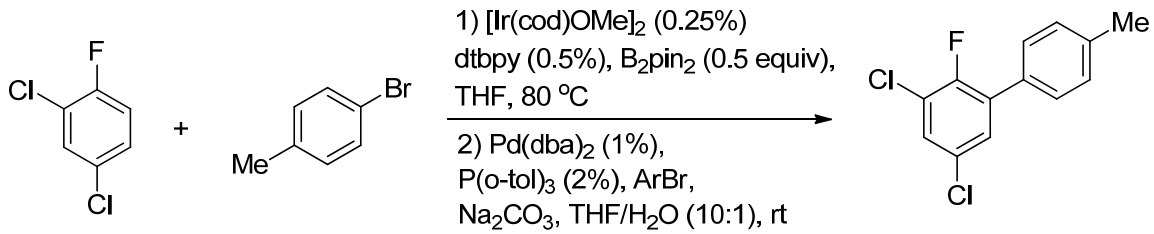


Arylation of 2-chloro-4-fluorotoluene with ethyl 4-bromobenzoate. Prepared according to the general procedure with 2-chloro-4-fluorotoluene (174 mg, 1.20 mmol, 1.20 equiv) and ethyl 4-bromobenzoate (229 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (237 mg, 81%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 7.56 (dd, J = 8.4, 1.7 Hz, 2H), 7.28 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 10.1 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.44, 157.84 (d, J = 249.8 Hz), 139.56 (d, J = 1.7 Hz), 134.65 (d, J = 10.2 Hz), 132.50 (d, J = 3.9 Hz), 132.27 (d, J = 3.7 Hz), 130.02, 129.91, 128.97 (d, J = 3.1 Hz), 126.66 (d, J = 13.0 Hz), 117.24 (d, J = 26.1 Hz), 61.25, 19.49, 14.56. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.26. Anal. Calcd for $C_{16}H_{14}ClFO_2$: C, 65.65; H, 4.82. Found: C, 65.51; H, 4.97.

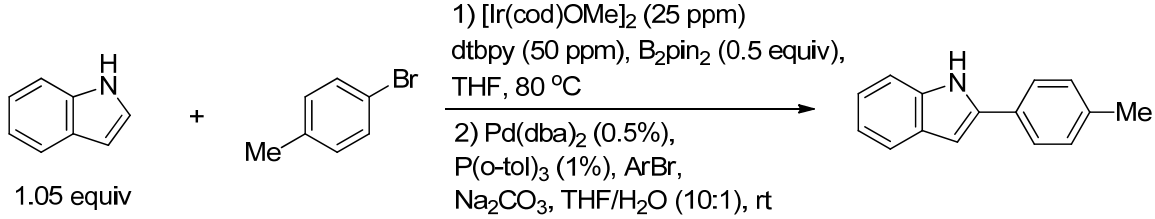


Arylation of 2-chloro-4-fluorotoluene with 4-bromoveratrole. Prepared according to the general procedure with 2-chloro-4-fluorotoluene (174 mg, 1.20 mmol, 1.20 equiv) and 4-bromoveratrole (217 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (278 mg, 99%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.2, 0.8 Hz, 1H), 7.14 (d, J = 10.2 Hz,

1H), 7.07 (t, *J* = 1.8 Hz, 1H), 7.05 (t, *J* = 1.5 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.79 (d, *J* = 247.9 Hz), 149.08 (d, *J* = 7.5 Hz), 133.22 (d, *J* = 10.1 Hz), 132.19 (d, *J* = 3.8 Hz), 132.15, 127.81, 127.50 (d, *J* = 13.2 Hz), 121.58 (d, *J* = 2.9 Hz), 117.14, 116.92, 112.33 (d, *J* = 3.2 Hz), 111.38, 56.16, 56.11, 19.52. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.64. Anal. Calcd for $C_{15}H_{14}ClFO_2$: C, 64.18; H, 5.03. Found: C, 64.18; H, 5.16.



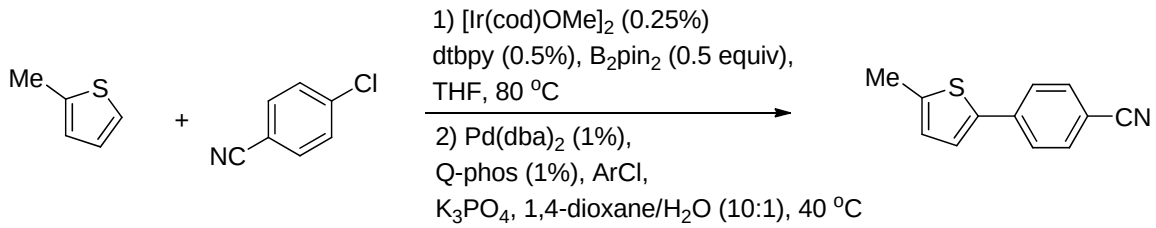
Arylation of 2,4-dichlorofluorobenzene with ethyl 4-bromobenzoate. Prepared according to the general procedure with 2,4-dichlorofluorobenzene (198 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (243 mg, 95%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.39 (dd, *J* = 5.9, 2.6 Hz, 1H), 7.34 (dd, *J* = 6.0, 2.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.29 (d, *J* = 249.9 Hz), 138.95, 131.98 (d, *J* = 15.1 Hz), 131.10, 129.67, 129.52 (d, *J* = 4.5 Hz), 129.02 (d, *J* = 3.1 Hz), 128.97 (d, *J* = 3.2 Hz), 128.90, 122.95 (d, *J* = 20.5 Hz), 21.49. ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.63. Anal. Calcd for $C_{13}H_9Cl_2F$: C, 61.20; H, 3.56. Found: C, 60.80; H, 3.44.



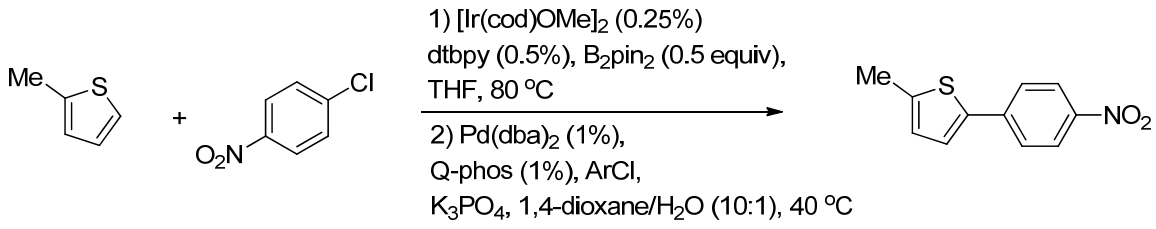
Arylation of indole with 4-bromotoluene on 5 mmol scale. Inside a glove box, $[Ir(cod)OMe]_2$ (0.9 mg, 0.001 mmol, 0.0003 equiv), dtbpy (0.8 mg, 0.002 mmol, 0.0005 equiv), B_2pin_2 (667 mg, 2.63 mmol, 0.525 equiv), indole (615 mg, 5.25 mmol, 1.05 equiv), and THF (10 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (14.4 mg, 0.025 mmol, 0.0050 equiv), tri-*o*-tolylphosphine (15.2 mg, 0.050 mmol, 0.010 equiv), 4-bromotoluene (855 mg, 5.00 mmol, 1.00 equiv), Na_2CO_3 (2.12 mg, 20.0 mmol, 20.0 equiv), THF (15 mL) and degassed H_2O (1.5 mL) were added to the reaction mixture. The reaction mixture was sealed and stirred at room temperature for 18 h. The reaction mixture was filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography (15% EtOAc:85% hexanes) to give the product (859 mg, 83%). Spectral data matched that obtained for the reaction conducted on 1 mmol scale.

General Procedure for one-pot C-H Borylation and Suzuki-Miyaura cross-coupling of heteroarenes with aryl chlorides. Inside a glove box, $[Ir(cod)OMe]_2$ (2.0 mg, 0.003 mmol, 0.003 equiv), dtbpy (1.6 mg, 0.0060 mmol, 0.0060 equiv), B_2pin_2 (153 mg, 0.600 mmol, 0.600 equiv), the heteroarene (1.20 mmol, 1.20 equiv), and THF (2 mL) were added to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.01 equiv), Q-phos (7.1 mg, 0.010 mmol, 0.010 equiv), the aryl chloride (1.00 mmol, 1.00 equiv), K_3PO_4 (849 mg, 4.00 mmol, 4.00 equiv), 1,4-dioxane (3 mL) and degassed H_2O (0.3 mL) were added to

the reaction mixture. The reaction mixture was sealed and stirred at 40 °C for 18 h. The reaction mixture was filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

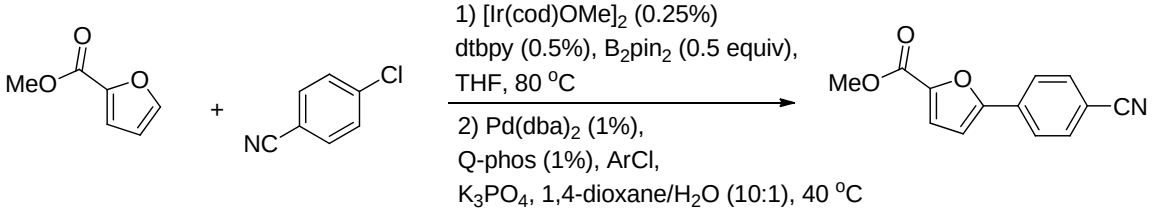


Arylation of 2-methylthiophene with 4-chlorobenzonitrile. Prepared according to the general procedure with 2-methylthiophene (152 mg, 1.20 mmol, 1.20 equiv) and 4-chlorobenzonitrile (138 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (157 mg, 79%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.59 (s, 4H), 7.21 (d, J = 3.5 Hz, 1H), 6.78 (s, 1H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.45, 139.78, 139.12, 132.85, 127.10, 125.69, 125.39, 119.21, 110.11, 15.79. Anal. Calcd for $C_{12}H_9NS$: C, 72.33; H, 4.55; N, 7.03. Found: C, 72.47; H, 4.58; N, 6.73.

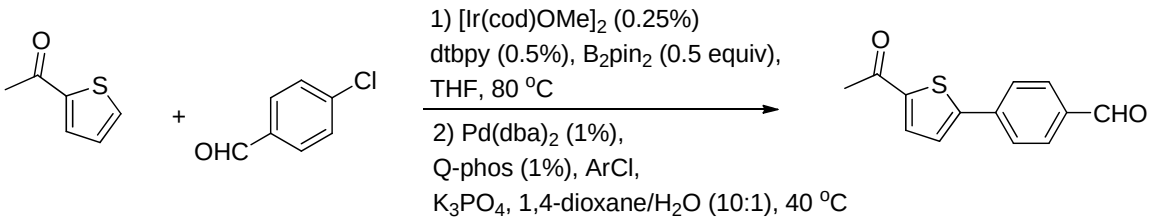


Arylation of 2-methylthiophene with 4-chloronitrobenzene. Prepared according to the general procedure with 2-methylthiophene (152 mg, 1.20 mmol, 1.20 equiv) and 4-chloronitrobenzene (158 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (178 mg, 79%).

^{1}H NMR (499 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 3.7 Hz, 1H), 6.79 (s, 1H), 2.54 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.39, 143.24, 141.07, 139.32, 127.29, 126.04, 125.53, 124.57, 15.81. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.35; H, 4.07; N, 6.52.

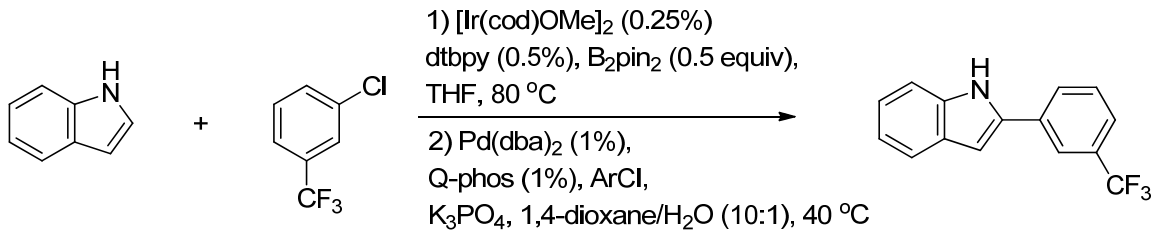


Arylation of methyl 2-furoate with 4-chlorobenzonitrile. Prepared according to the general procedure with methyl 2-furoate (151 mg, 1.20 mmol, 1.20 equiv) and 4-chlorobenzonitrile (138 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (218 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 3.6 Hz, 1H), 6.88 (d, *J* = 3.7 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.07, 155.25, 145.08, 133.47, 132.89, 125.28, 120.08, 118.74, 112.23, 109.73, 52.34. Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.56; H, 3.87; N, 6.46.

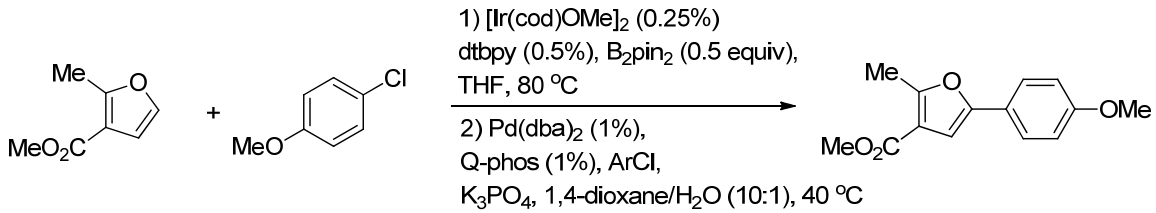


Arylation of 2-acetylthiophene with 4-chlorobenzaldehyde. Prepared according to the general procedure with 2-acetylthiophene (152 mg, 1.20 mmol, 1.20 equiv) and 4-chlorobenzaldehyde (141 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (210 mg, 91%).

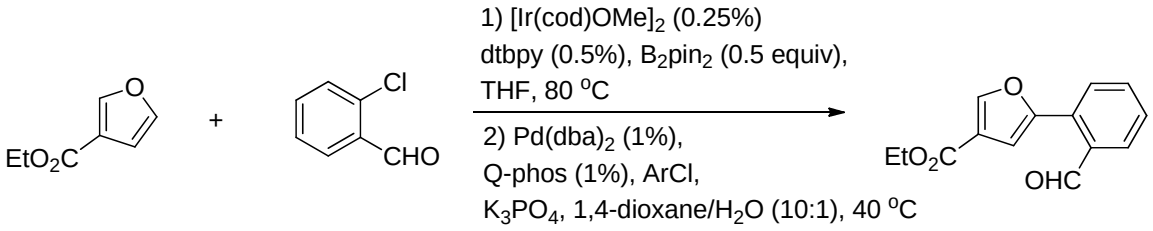
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 3.9 Hz, 1H), 7.42 (d, *J* = 3.8 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.57, 190.84, 150.60, 144.90, 138.99, 136.34, 133.68, 130.71, 126.80, 125.88, 25.04. Anal. Calcd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38. Found: C, 67.86; H, 4.38.



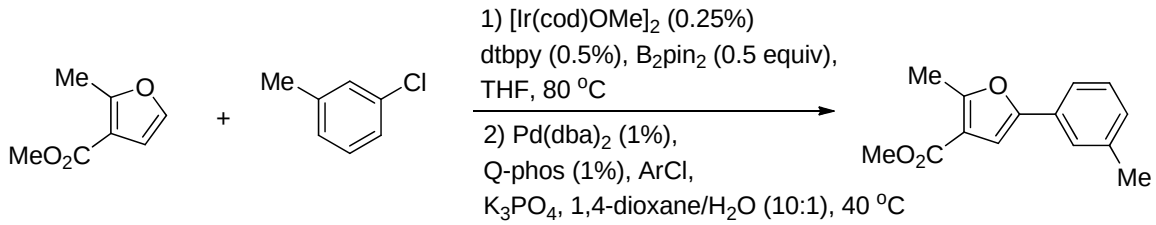
Arylation of indole with 3-chlorobenzotrifluoride. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 3-chlorobenzotrifluoride (181 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (235 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.89 (s, 1H), 7.80 (d, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.57 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.26 (m, 1H), 7.19 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.91 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.33 (s), 136.48 (s), 133.41 (s), 131.70 (q, *J* = 32.4 Hz), 129.76 (s), 129.31 (s), 128.47 (s), 124.37 (q, *J* = 3.7 Hz), 124.32 (q, *J* = 272 Hz), 123.27 (s), 121.97 (q, *J* = 3.8 Hz), 121.22 (s), 120.86 (s), 111.39 (s), 101.48 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.28 (s). Anal. Calcd for $C_{15}H_{10}F_3N$: C, 68.96; H, 3.86; N, 5.36. Found: C, 69.26; H, 3.91; N, 5.29.



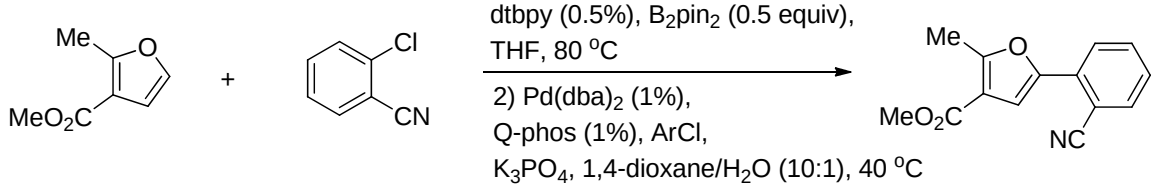
Arylation of methyl 2-methyl-3-furancarboxylate with 4-chloroanisole. Prepared according to the general procedure with methyl 2-methyl-3-furancarboxylate (168 mg, 1.20 mmol, 1.20 equiv) and 4-chloroanisole (143 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (133 mg, 54%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.57 (s, 2H), 6.91 (s, 1H), 6.74 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.78, 159.49, 158.32, 152.08, 125.34, 123.29, 115.21, 114.39, 103.96, 55.51, 51.54, 14.04. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.64; H, 5.80.



Arylation of ethyl 3-furoate with 2-chlorobenzaldehyde. Prepared according to the general procedure with ethyl 3-furoate (168 mg, 1.20 mmol, 1.20 equiv) and 2-chlorobenzaldehyde (141 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (144 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (d, J = 0.8 Hz, 1H), 8.13 (d, J = 0.8 Hz, 1H), 7.95 (d, J = 1.3 Hz, 1H), 7.63 (m, 2H), 7.47 (m, 1H), 6.94 (d, J = 0.8 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.74, 162.85, 152.37, 148.48, 133.91, 133.51, 132.33, 129.11, 128.90, 128.49, 121.79, 110.86, 60.99, 14.55. Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.59; H, 4.82.

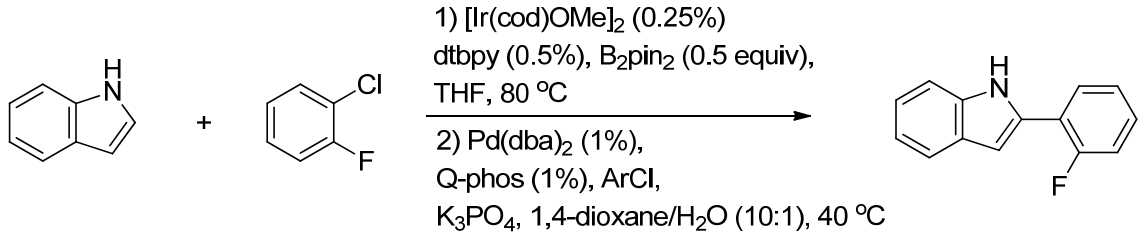


Arylation of methyl 2-methyl-3-furancarboxylate with 3-chlorotoluene. Prepared according to the general procedure with methyl 2-methyl-3-furancarboxylate (168 mg, 1.20 mmol, 1.20 equiv) and 3-chlorotoluene (127 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (133 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.86 (s, 1H), 3.85 (s, 3H), 2.65 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.71, 158.85, 152.15, 138.56, 130.15, 128.85, 128.69, 124.47, 121.04, 115.28, 105.50, 51.58, 21.69, 14.09. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.79; H, 6.13.

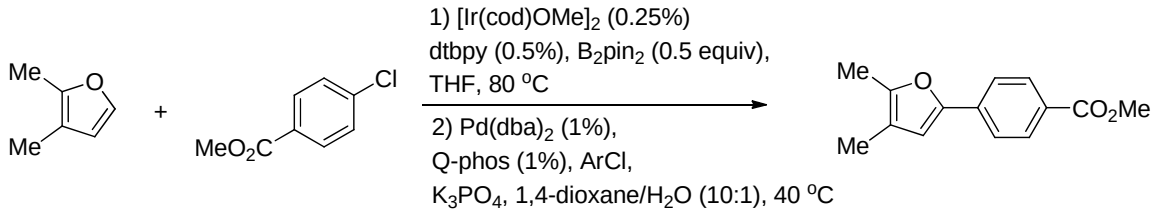


Arylation of methyl 2-methyl-3-furancarboxylate with 2-chlorobenzonitrile. Prepared according to the general procedure with methyl 2-methyl-3-furancarboxylate (168 mg, 1.20 mmol, 1.20 equiv) and 2-chlorobenzonitrile (138 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (20% EtOAc:80% hexanes) to give the product (193 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 1H), 7.65 (m, 1H), 7.57 (td, J = 7.8, 1.4 Hz, 1H), 7.43 (s, 1H), 7.30 (m, 1H), 3.82 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.08, 160.22, 147.70, 134.40,

133.15, 132.45, 127.64, 125.92, 118.80, 115.85, 110.95, 106.95, 51.71, 14.01. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.46; H, 4.47; N, 5.74.



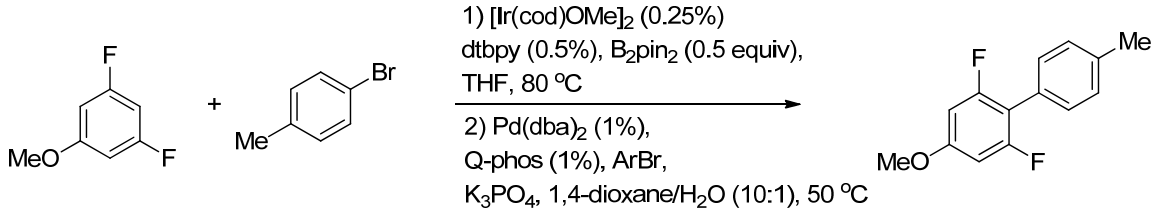
Arylation of indole with 2-fluorochlorobenzene. Prepared according to the general procedure with indole (141 mg, 1.20 mmol, 1.20 equiv) and 2-fluorochlorobenzene (131 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (15% EtOAc:85% hexanes) to give the product (127 mg, 60%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.82 (dd, *J* = 8.8, 6.9 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.27 (m, 5H), 7.03 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.60 (d, *J* = 246.4 Hz), 136.93 (d, *J* = 1.6 Hz), 132.89 (d, *J* = 2.4 Hz), 129.10 (d, *J* = 8.9 Hz), 128.49 (s), 128.25 (d, *J* = 4.0 Hz), 125.09 (d, *J* = 3.1 Hz), 122.99 (s), 120.99 (s), 120.55 (s), 120.24 (s), 116.80 (d, *J* = 23.0 Hz), 111.36 (s), 101.97 (d, *J* = 3.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.86 (s). Anal. Calcd for $C_{14}H_{10}FN$: C, 79.60; H, 4.77; N, 6.63. Found: C, 79.22; H, 4.72; N, 6.42.



Arylation of 2,3-dimethylfuran with methyl 4-chlorobenzoate. Prepared according to the general procedure with 2,3-dimethylfuran (116 mg, 1.20 mmol, 1.20 equiv) and methyl 4-chlorobenzoate (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by

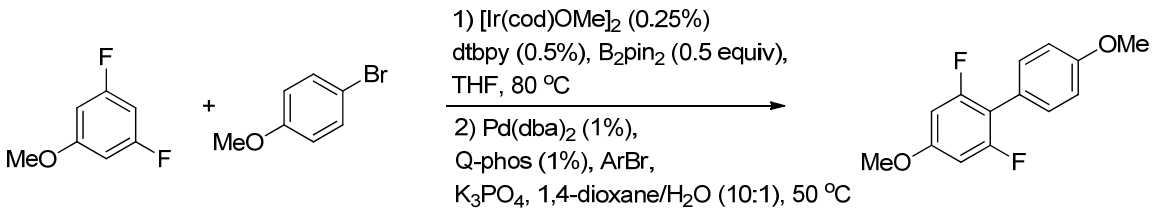
flash column chromatography (10% EtOAc:90% hexanes) to give the product (184 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 6.55 (s, 1H), 3.89 (s, 3H), 2.27 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.16, 150.04, 149.05, 135.35, 130.25, 127.83, 122.85, 116.98, 111.06, 52.20, 11.77, 10.10. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.93; H, 6.28.

General Procedure for one-pot C-H Borylation and Suzuki-Miyaura cross-coupling of 3,5-difluoroarenes with aryl bromides. Inside a glove box, $[Ir(cod)OMe]_2$ (2.0 mg, 0.003 mmol, 0.003 equiv), dtbpy (1.6 mg, 0.0060 mmol, 0.0060 equiv), B_2pin_2 (183 mg, 0.720 mmol, 0.720 equiv), the arene (1.20 mmol, 1.20 equiv), and THF (2 mL) were added consecutively to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed under vacuum. $Pd(dba)_2$ (5.8 mg, 0.010 mmol, 0.010 equiv), Q-phos (7.1 mg, 0.010 mmol, 0.010 equiv), the aryl bromide (1.00 mmol, 1.00 equiv), K_3PO_4 (849 mg, 4.00 mmol, 4.00 equiv), 1,4-dioxane (3 mL) and degassed H_2O (0.3 mL) were added consecutively to the reaction mixture. The reaction mixture was sealed and stirred at 50 °C for 18 h. The reaction mixture was filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product.

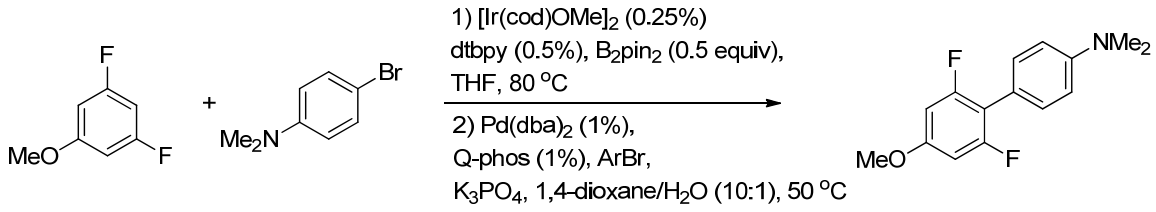


Arylation of 3,5-difluoroanisole with 4-bromotoluene. Prepared according to the general procedure with 3,5-difluoroanisole (173 mg, 1.20 mmol, 1.20 equiv) and 4-

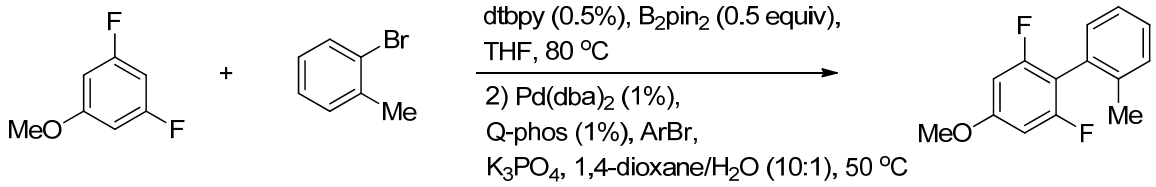
bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (180 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 6.59 (d, *J* = 9.3 Hz, 2H), 3.84 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.94 (dd, J = 246.96 Hz, 10.46 Hz), 160.094 (t, *J* = 14.24 Hz), 137.85 (s), 130.45 (s), 129.24 (s), 126.57 (s), 111.21 (t, *J* = 19.6 Hz), 98.39 (m), 55.96 (s), 21.50 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.24 (s). Anal. Calcd for $C_{14}H_{12}F_2O$: C, 71.79; H, 5.16. Found: C, 71.87; H, 5.24.



Arylation of 3,5-difluoroanisole with 4-bromoanisole. Prepared according to the general procedure with 3,5-difluoroanisole (173 mg, 1.20 mmol, 1.20 equiv) and 4-bromoanisole (187 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (185 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 9.5 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.91 (dd, J = 245.70 Hz, 10.46 Hz), 159.901 (t, *J* = 14.24 Hz), 159.42 (s), 131.70 (s), 121.71 (s), 114.00 (s), 110.88 (t, *J* = 19.4 Hz), 98.37 (m), 55.95 (s), 55.45 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.35 (s). Anal. Calcd for $C_{14}H_{12}F_2O_2$: C, 67.20; H, 4.83. Found: C, 67.52; H, 4.66.

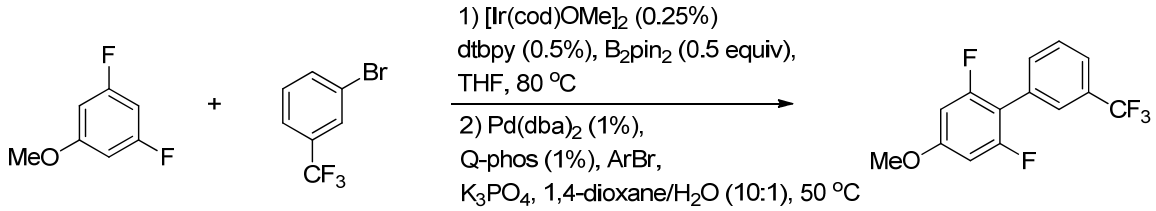


Arylation of 3,5-difluoroanisole with 4-bromo-*N*,*N*-dimethylaniline. Prepared according to the general procedure with 3,5-difluoroanisole (173 mg, 1.20 mmol, 1.20 equiv) and 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (192 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 9.5 Hz, 2H), 3.83 (s, 3H), 3.03 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.00 (dd, J = 245.2, 10.6 Hz), 159.39 (t, J = 14.2 Hz), 150.19 (s), 131.25 (s), 117.03 (s), 112.31 (s), 111.44 (t, J = 19.5 Hz), 98.34 (m), 55.97 (s), 40.67 (s).^{19}F NMR (376 MHz, $CDCl_3$) δ -114.36 (s). Anal. Calcd for $C_{15}H_{15}F_2NO$: C, 68.43; H, 5.74; N, 5.32. Found: C, 68.80; H, 5.80; N, 5.14.

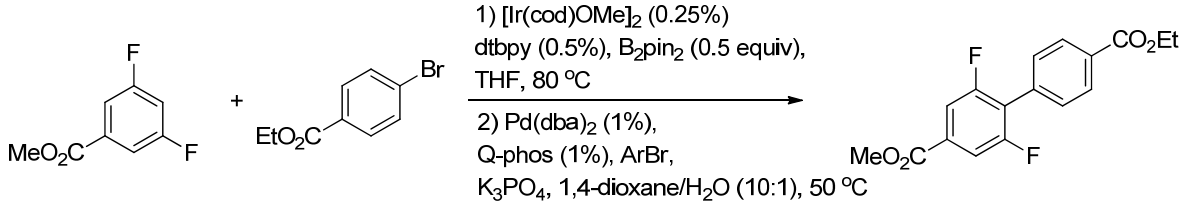


Arylation of 3,5-difluoroanisole with 2-bromotoluene. Prepared according to the general procedure with 3,5-difluoroanisole (173 mg, 1.20 mmol, 1.20 equiv) and 2-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (164 mg, 70%). 1H NMR (500 MHz, CDCl3) δ 7.34 (s, 2H), 7.28 (m, 3H), 6.59 (d, J = 9.1 Hz, 1H), 3.85 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.87 (dd, J = 245.83, 10.96),

160.55 (t, J = 13.8 Hz), 137.96 (s), 131.27 (s), 130.29 (s), 129.17 (s), 128.66 (s), 125.79 (s), 110.63 (t, J = 22.1 Hz), 98.13 (m), 56.00 (s), 20.03 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.03 (s). Anal. Calcd for $C_{14}H_{15}F_2O$: C, 71.78; H, 5.16. Found: C, 72.00; H, 5.00.

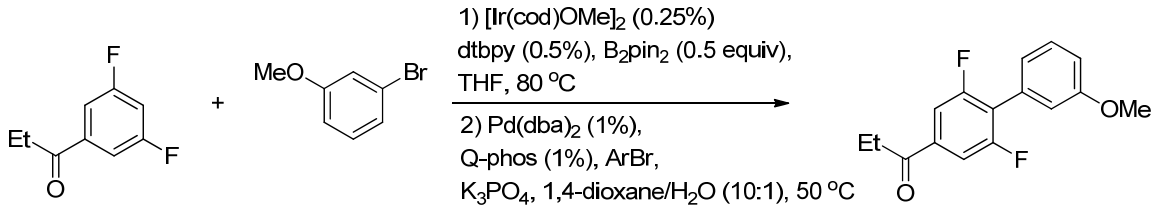


Arylation of 3,5-difluoroanisole with 3-bromobenzotrifluoride. Prepared according to the general procedure with 3,5-difluoroanisole (173 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (225 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (5% EtOAc:95% hexanes) to give the product (259 mg, 90%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.66 (d, J = 7.4 Hz, 2H), 7.57 (m, 1H), 6.60 (d, J = 9.7 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.91 (t, J = 14.2 Hz), 160.78 (dd, J = 248.22 Hz, 10.08 Hz), 133.93 (s), 130.94 (q, J = 32.3 Hz), 130.49 (s), 128.92 (s), 127.38 (dt, J = 3.9, 2.1 Hz), 124.72 (q, J = 3.8 Hz), 124.36 (q, J = 273 Hz), 109.69 (t, J = 18.9 Hz), 98.56 (m), 55.99 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.13 (s), -114.33 (s). Anal. Calcd for $C_{14}H_9F_5O$: C, 58.34; H, 3.15. Found: C, 58.61; H, 3.43.

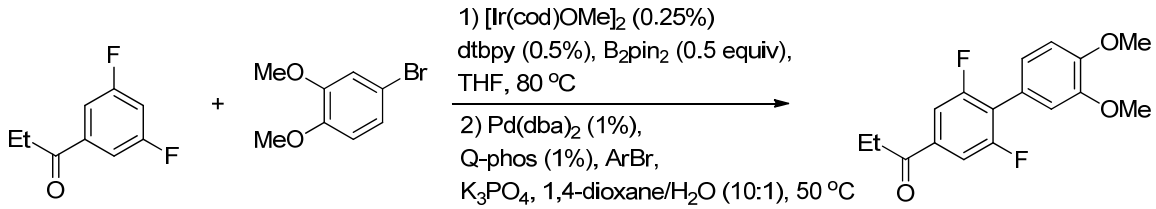


Arylation of methyl 3,5-difluorobenzoate with ethyl 4-bromobenzoate. Prepared according to the general procedure with methyl 3,5-difluorobenzoate (207 mg, 1.20 mmol, 1.20 equiv) and ethyl 4-bromobenzoate (229 mg, 1.00 mmol, 1.00 equiv). The mixture

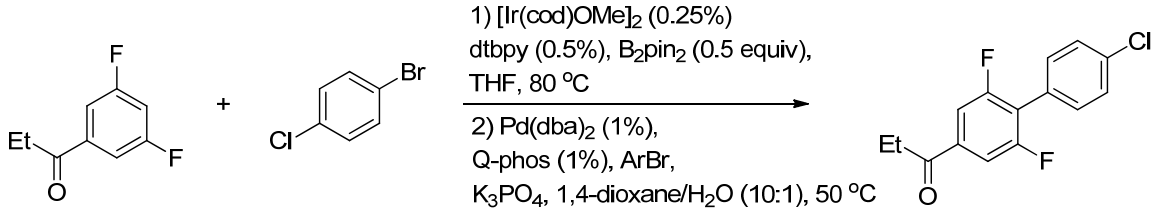
was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (269 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.21 (s), 164.81 (t, *J* = 3.2 Hz), 159.79 (dd, *J* = 250.8, 6.8 Hz), 132.92 (s), 131.97 (t, *J* = 9.6 Hz), 130.95 (s), 130.41 (s), 129.68 (s), 122.14 (t, *J* = 18.5 Hz), 113.26 (m), 61.36 (s), 52.91 (s), 14.51 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.08 (s). Anal. Calcd for $C_{17}H_{14}F_2O_4$: C, 63.75; H, 4.41. Found: C, 63.86; H, 4.37.



Arylation of 3,5-difluoropropiophenone with 3-bromoanisole. Prepared according to the general procedure with 3,5-difluoropropiophenone (204 mg, 1.20 mmol, 1.20 equiv) and 3-bromoanisole (187 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (199 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.06 (m, 1H), 7.02 (d, *J* = 1.3 Hz, 1H), 6.98 (m, 1H), 3.83 (s, 3H), 2.97 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.07 (s), 160.23 (dd, *J* = 245.70 Hz, 6.80 Hz), 159.68 (s), 137.80 (t, *J* = 7.8 Hz), 129.63 (s), 123.05 (s), 122.90 (s), 122.72 (s), 116.03 (s), 114.67 (s), 111.51 (m), 55.51 (s), 32.13 (s), 8.23 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.67 (s). Anal. Calcd for $C_{16}H_{14}F_2O_2$: C, 69.56; H, 5.11. Found: C, 69.59; H, 5.08.

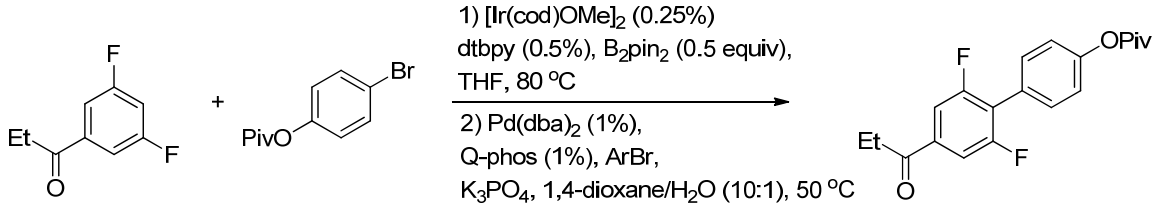


Arylation of 3,5-difluoropropiophenone with 4-bromoveratrole. Prepared according to the general procedure with 3,5-difluoropropiophenone (204 mg, 1.20 mmol, 1.20 equiv) and 4-bromoveratrole (217 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (187 mg, 61%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.53 (d, J = 7.7 Hz, 2H), 7.05 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.94 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.03 (s), 160.22 (dd, J = 249.8, 6.9 Hz), 149.78 (s), 148.97 (s), 137.25 (t, J = 7.8 Hz), 123.31 (s), 122.84 (t, J = 18.6 Hz), 120.70 (s), 113.54 (s), 111.50 (m), 111.21 (s), 56.18 (s), 56.08 (s), 32.06 (s), 8.23 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.05 (s). Anal. Calcd for $C_{20}H_{20}F_2O_3$: C, 69.35; H, 5.82. Found: C, 69.20; H, 5.62.

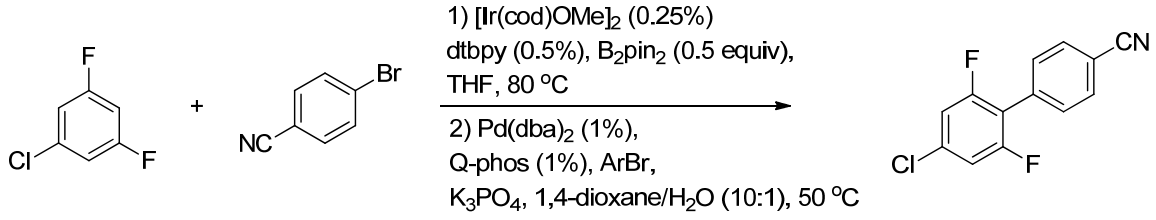


Arylation of 3,5-difluoropropiophenone with 4-chlorobromobenzene. Prepared according to the general procedure with 3,5-difluoropropiophenone (204 mg, 1.20 mmol, 1.20 equiv) and 4-chlorobromobenzene (192 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (185 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7 Hz, 2H), 7.42 (d, J = 3.2 Hz, 4H), 2.97 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 197.98 (s), 160.11 (dd, *J* = 251.0, 6.7 Hz), 138.04 (t, *J* = 7.81 Hz), 135.27 (s), 131.72 (s), 128.95 (s), 126.85 (s), 121.82 (t, *J* = 18.7 Hz), 111.60 (m), 32.17 (s), 8.24 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.11 (m). Anal. Calcd for $C_{15}H_{11}ClF_2O$: C, 64.18; H, 3.95. Found: C, 64.29; H, 4.07.

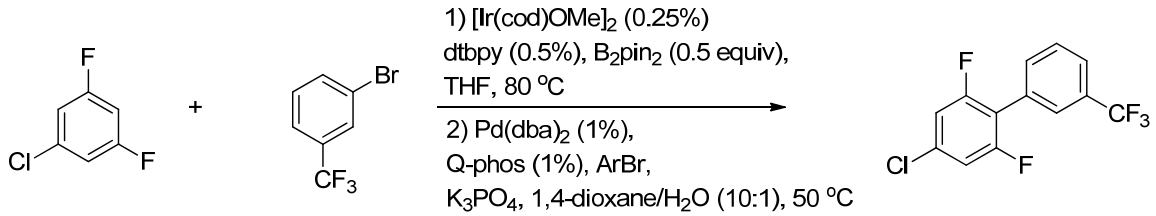


Arylation of 3,5-difluoropropiophenone with 4-bromophenyl pivalate. Prepared according to the general procedure with 3,5-difluoropropiophenone (204 mg, 1.20 mmol, 1.20 equiv) and 4-bromophenyl pivalate (257 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (194 mg, 56%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.37 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.05 (s), 177.02 (s), 160.22 (dd, *J* = 250.8, 6.8 Hz), 151.71 (s), 137.81 (t, *J* = 7.8 Hz), 132.57 (s), 131.53 (s), 125.72 (s), 121.80 (s), 111.55 (m), 39.38 (s), 32.14 (s), 27.33 (s), 8.25 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.99 (s). Anal. Calcd for $C_{17}H_{16}F_2O_3$: C, 66.66; H, 5.26. Found: C, 66.45; H, 5.07.

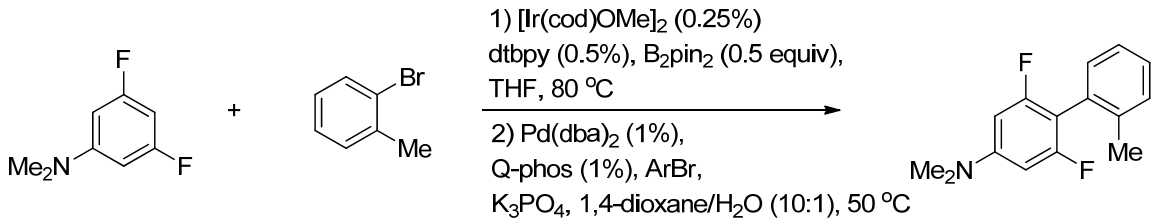


Arylation of 3,5-difluorochlorobenzene with 4-bromobenzonitrile. Prepared according to the general procedure with 3,5-difluorochlorobenzene (179 mg, 1.20 mmol,

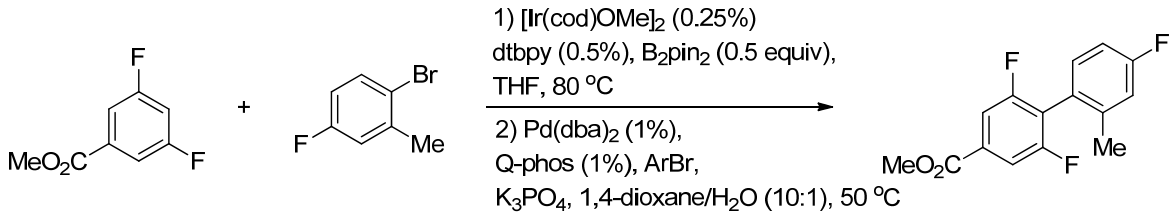
1.20 equiv) and 4-bromobenzonitrile (182 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (192 mg, 77%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.57 (m, 2H), 7.07 (d, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.85 (dd, J = 252.6, 7.9 Hz), 135.63 (t, J = 13.4 Hz), 133.28 (s), 132.30 (s), 131.19 (s), 118.58 (s), 115.82 (t, J = 18.6 Hz), 113.36 (m), 112.71 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.95 (s). Anal. Calcd for $C_{13}H_6ClF_2N$: C, 62.54; H, 2.42; N, 5.61. Found: C, 62.34; H, 2.36; N, 5.42.



Arylation of 3,5-difluorochlorobenzene with 3-bromobenzotrifluoride. Prepared according to the general procedure with 3,5-difluorochlorobenzene (179 mg, 1.20 mmol, 1.20 equiv) and 3-bromobenzotrifluoride (225 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (196 mg, 67%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (d, J = 7.0 Hz, 1H), 7.64 (m, 1H), 7.60 (m, 1H), 7.08 (d, J = 7.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.00 (dd, J = 252.1, 8.3 Hz), 135.03 (t, J = 13.4 Hz), 133.75 (s), 131.20 (q, J = 32.5 Hz), 129.29 (s), 129.14 (s), 127.24 (m), 125.56 (q, J = 3.7 Hz), 124.16 (q, J = 273 Hz), 116.19 (t, J = 18.6 Hz), 113.27 (m). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.20 (s), -113.16 (s). Anal. Calcd for $C_{13}H_6ClF_5$: C, 53.36; H, 2.07. Found: C, 53.09; H, 2.35.

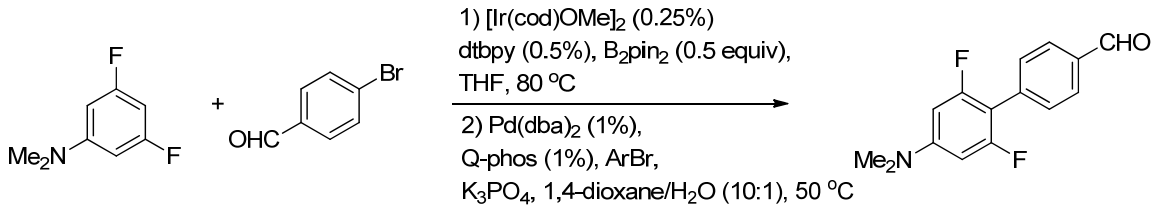


Arylation of 3,5-difluoro-*N,N*-dimethylaniline with 2-bromotoluene. Prepared according to the general procedure with 3,5-difluoro-*N,N*-dimethylaniline (189 mg, 1.20 mmol, 1.20 equiv) and 2-bromotoluene (182 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (232 mg, 94%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.34 (s, 1H), 6.37 (d, J = 10.9 Hz, 2H), 3.03 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.28 (dd, J = 242.3, 11.6 Hz), 151.34 (t, J = 13.4 Hz), 138.26 (s), 131.63 (s), 130.26 (s), 130.06 (s), 128.29 (s), 125.73 (s), 105.53 (t, J = 22.4 Hz), 95.20 (m), 40.44 (s), 20.21 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.47 (s). Anal. Calcd for $C_{15}H_{15}F_2N$: C, 72.86; H, 6.11; N, 5.66. Found: C, 73.06; H, 6.20; N, 5.66.

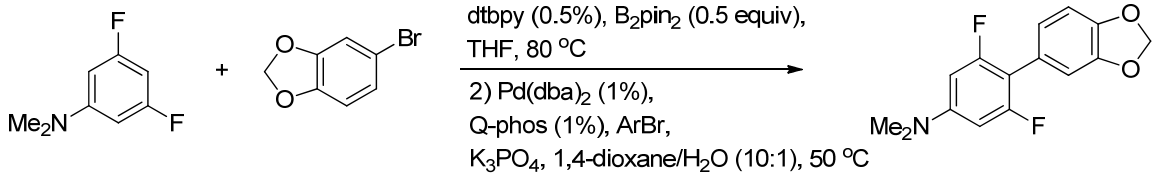


Arylation of methyl 3,5-difluorobenzoate with 2-bromo-5-fluorotoluene. Prepared according to the general procedure with methyl 3,5-difluorobenzoate (207 mg, 1.20 mmol, 1.20 equiv) and 2-bromo-5-fluorotoluene (189 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (163 mg, 58%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.68 (d, J = 7.4 Hz, 2H), 7.28 (m, 1H), 7.07 (td, J = 8.4, 2.8 Hz, 1H), 6.96 (dd, J = 9.0, 2.7 Hz, 1H), 3.97 (s, 3H), 2.13 (s,

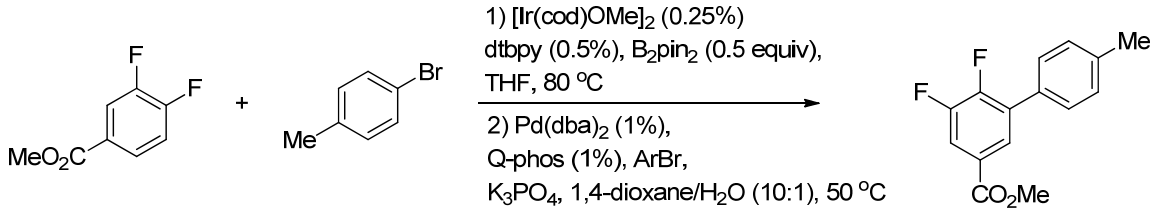
3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.01 (t, *J* = 3.4 Hz), 160.89 (d, *J* = 245.32 Hz), 159.92 (dd, *J* = 250.74 Hz, 7.2 Hz), 133.04 (d, *J* = 3.4 Hz), 132.29 (t, *J* = 9.5 Hz), 131.78 (d, *J* = 7.9 Hz), 129.65 (d, *J* = 8.2 Hz), 121.91 (t, *J* = 21.4 Hz), 117.28 (d, *J* = 22.3 Hz), 116.14 (d, *J* = 20.6 Hz), 113.03 (m), 52.94 (s), 19.10 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.12 (s), -118.26 (s). Anal. Calcd for $C_{15}H_{11}F_3O_2$: C, 64.29; H, 3.96. Found: C, 64.30; H, 3.82.



Arylation of 3,5-difluoro-*N,N*-dimethylaniline with 4-bromobenzaldehyde. Prepared according to the general procedure with 3,5-difluoro-*N,N*-dimethylaniline (189 mg, 1.20 mmol, 1.20 equiv) and 4-bromobenzaldehyde (185 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (186 mg, 71%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.90 (s, 2H), 7.63 (s, 2H), 6.27 (s, 2H), 2.99 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.11 (s), 161.17 (dd, *J* = 244.9, 10.8 Hz), 151.60 (t, *J* = 13.8 Hz), 137.23 (s), 134.97 (s), 131.05 (t, *J* = 2.6 Hz), 129.62 (s), 104.47 (t, *J* = 18.7 Hz), 95.45 (m), 40.26 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.20 (s). Anal. Calcd for $C_{15}H_{13}F_2NO$: C, 68.96; H, 5.02; N, 5.36. Found: C, 68.65; H, 4.89; N, 5.09.

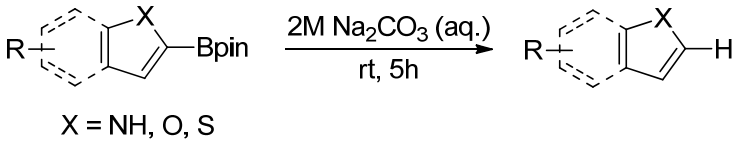


Arylation of 3,5-difluoro-*N,N*-dimethylaniline with 1-Bromo-3,4-(methylenedioxy)benzene. Prepared according to the general procedure with 3,5-difluoro-*N,N*-dimethylaniline (189 mg, 1.20 mmol, 1.20 equiv) and 1-Bromo-3,4-(methylenedioxy)benzene (201 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (177 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (m, 2H), 6.87 (m, 1H), 6.27 (d, *J* = 11.5 Hz, 2H), 5.99 (s, 2H), 2.97 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.16 (dd, *J* = 243.0, 10.8 Hz), 150.75 (t, *J* = 13.5 Hz), 147.59 (s), 146.90 (s), 124.17 (s), 123.78 (s), 111.08 (s), 108.36 (s), 105.61 (t, *J* = 19.9 Hz), 101.24 (s), 95.47 (m), 40.40 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.56 (m). . Calcd for $C_{15}H_{13}F_2NO_2$: C, 64.98; H, 4.73; N, 5.05. Found: C, 64.97; H, 4.59; N, 4.82.

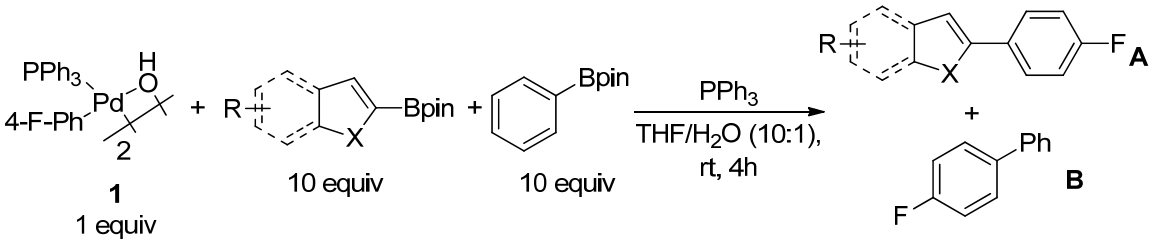


Arylation of methyl 3,4-difluorobenzoate with 4-bromotoluene. Prepared according to the general procedure with methyl 3,4-difluorobenzoate (207 mg, 1.20 mmol, 1.20 equiv) and 4-bromotoluene (171 mg, 1.00 mmol, 1.00 equiv). The mixture was purified by flash column chromatography (10% EtOAc:90% hexanes) to give the product (231 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (m, 1H), 7.80 (m, 1H), 7.46 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.28 (m, 2H), 3.93 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.49 (d, *J* = 2.6 Hz), 151.20 (dd, *J* = 250.74, 6.43 Hz), 150.93 (dd, *J* = 248.72, 12.85 Hz), 138.88, 131.50 (d, *J* = 11.0 Hz), 131.00 (d, *J* = 2.6 Hz), 129.66 , 128.97 (d, *J* = 3.1 Hz), 127.26 (t, *J* = 3.2 Hz), 126.63 (dd, *J* = 6.6, 4.2 Hz), 117.15 (m), 52.72, 21.45. ^{19}F NMR

(376 MHz, $CDCl_3$) δ -136.27 (d, *J* = 20.0 Hz), -136.70 (dd, *J* = 20.6, 10.4 Hz). Anal. Calcd for $C_{15}H_{12}F_2O_2$: C, 68.70; H, 4.61. Found: C, 68.73; H, 4.56.

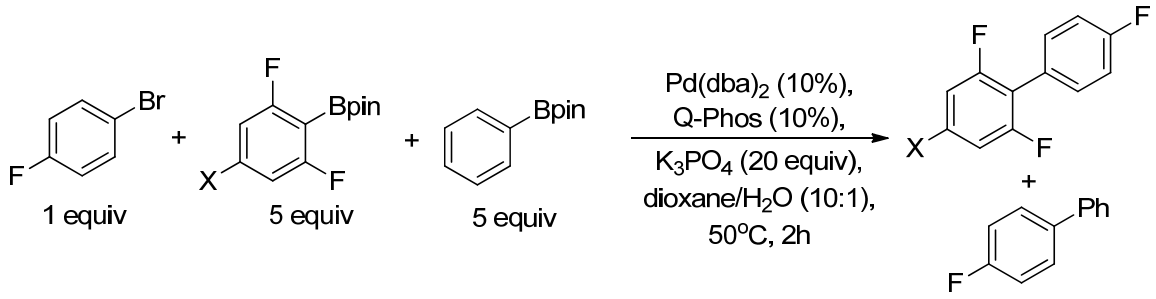


General Procedure for (hetero)aryl Bpin stability studies. Into a vial with a magnetic stir bar were added the (hetero)aryl Bpin (0.1 mmol), THF (0.3 mL), 2M aqueous Na_2CO_3 and 1,3,5-trimethoxybenzene (10 mg). The vial was sealed and was allowed to stir at room temperature for 5 hours. At this time, a sample was removed and analyzed using gas chromatography. The conversion of the (hetero)aryl Bpin was determined by comparison to the internal standard.



General Procedure for competition experiments between heteroaryl pinacol boronate esters and phenyl pinacol boronate. Inside a glove box, Pd complex **1** (9.6 mg, 0.010 mmol, 1.0 equiv), heteroaryl Bpin (0.100 mmol, 10.0 equiv), PhBpin (20.4 mg, 0.100 mmol, 10.0 equiv), PPh_3 (15.9 mg, 0.0600 mmol, 6.00 equiv), THF (0.25 mL), H_2O (0.025 mL), and 1,3,5-trimethoxybenzene (10 mg) were added to a dry vial equipped with a magnetic stir bar. The reaction mixture was sealed and stirred at room temperature for 5 h. At this time, a sample was removed and the yields of the 2-aryl-

heteroarene and 4-fluorobiphenyl were determined using gas chromatography by comparison to the internal standard.



General Procedure for competition experiments between 2,6-difluoroaryl pinacol boronate esters and phenyl pinacol boronate. Inside a glove box, $Pd(dba)_2$ (2.3 mg, 0.0040 mmol, 0.10 equiv), Q-phos (2.9 mg, 0.0040, 0.10 equiv), 2,6-difluoroaryl Bpin (0.200 mmol, 5.00 equiv), PhBpin (40.8 mg, 0.200 mmol, 5.00 equiv), 1-bromo-4-fluorobenzene (7.0 mg, 0.040 mmol, 1.0 equiv), K_3PO_4 (170 mg, 0.80 mmol, 20 equiv), 1,4-dioxane (0.5 mL), H_2O (0.05 mL), and 1,3,5-trimethoxybenzene (10 mg) were added to a dry vial equipped with a magnetic stir bar. The reaction mixture was sealed and stirred at 50 °C for 2 h. At this time, a sample was removed and the yields of the 2,6-difluorobiaryl and 4-fluorobiphenyl were determined using gas chromatography by comparison to the internal standard.

4.6 References

(1) a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633; b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(2) a) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555; b) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440; c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461; d) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(3) a) Darses, S.; Genet, J.-P. *Chem. Rev.* **2007**, *108*, 288; b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(4) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 928.

(5) a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358; b) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695.

(6) a) Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314; b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

(7) a) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073; b) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768.

(8) a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116; b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492.

(9) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(10) a) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2008**, *11*, 345; b) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381.

(11) a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508; b) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589; c) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350.

(12) a) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103; b) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

(13) a) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4841; b) Chotana, G. A.; Kallepalli, V. A.; Maleczka Jr, R. E.; Smith III, M. R. *Tetrahedron* **2008**, *64*, 6103; c) Asano, S.; Kamioka, S.; Isobe, Y. *Tetrahedron* **2012**, *68*, 272.

(14) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2010**, *111*, 1346.

(15) This finding with the boronic esters is consistent with previously reported kinetic data on transmetallation of fluorinated aryl boronic acids. See reference 6a.

(16) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

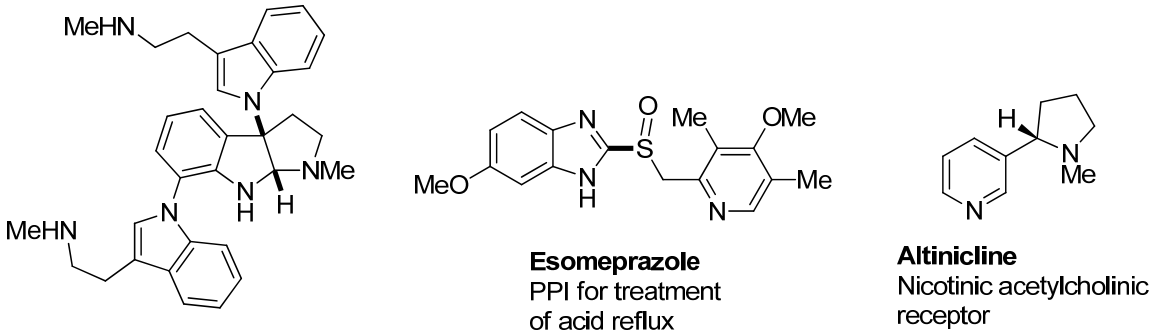
(17) Driver, M. S.; Hartwig, J. F. *Organometallics* **1997**, *16*, 5706.

(18) a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *124*, 390; b) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.

Chapter 5. Iridium-Catalyzed, Silyl-Directed C-H Borylation of Nitrogen-Containing Heterocycles

5.1 Introduction

Nitrogen-containing heterocycles constitute core structures in many molecules of tremendous importance, including electronic materials, natural products and pharmaceutical molecules with a wide range of biological activity (Scheme 47). Because of their importance, many methods for the synthesis and functionalization of this class of molecules have been developed.[1] Selective methods for the direct functionalization of nitrogen heterocycles could lead to rapid access to materials that are cumbersome to prepare by classical methods. To develop these selective and direct functionalization methods, transition metal catalysis presents a promising approach for the introduction of a variety of functionality with control of the site-selectivity of heteroarenes functionalization.

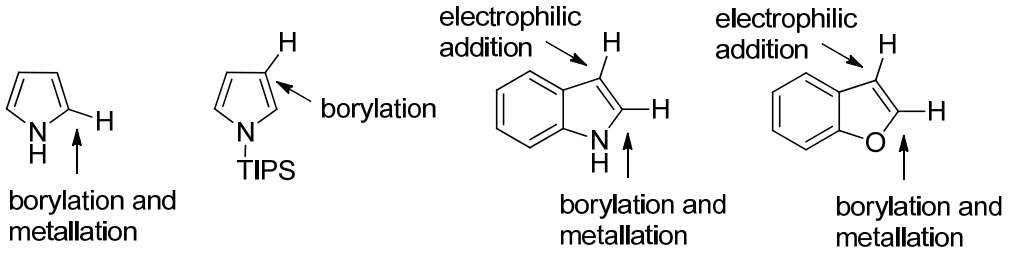


Scheme 47. Important nitrogen-containing heterocycles with biological activity

5.2 Background

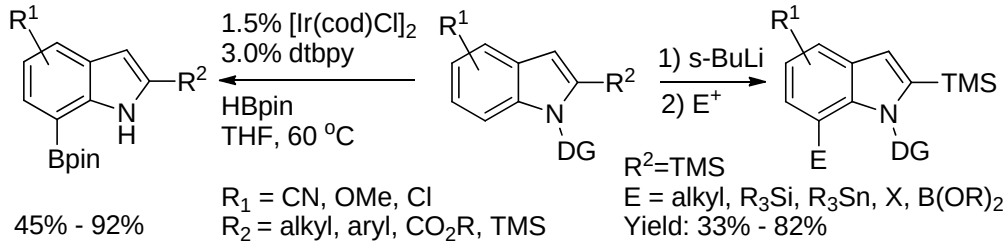
Although progress has been made,[1a,1b] few systems selectively functionalization the benzo-fused aromatic ring of indoles and related heterocycles due to the greater reactivity of the azole ring (Scheme 48),[2] and the selective functionalization of other biologically

important nitrogen-containing heterocycles, such as carbazoles and tetrahydroquinolines,[3] has been less studied. Some chloroperoxidases form 7-chloroindoles, but these reactions have not been reported on a synthetic scale or with a scope beyond tryptophan[4] or the parent indole.[5]



Scheme 48. Site-selectivity for borylation and metallation of heteroarenes

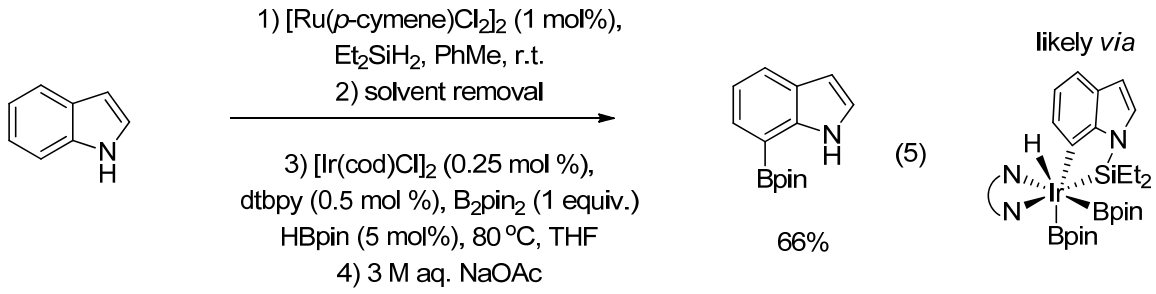
Selective functionalization of the 7-position of an indole by chemical methods typically requires a substituent at the 2-position to block reactivity at this site (Scheme 49). The borylation of indoles at the 7-position would create a method to prepare a variety of 7-indole derivatives by exploiting the reactivity of the heteroarylboronate products. Because the 2-position of indole is inherently the most reactive site for metallation,[6] the existing direct borylations of indoles at the 7-position[7] or indirect borylations by initial 7-lithiation of *N*-carbamoyl indoles have been conducted with 2-substituted derivatives.[8] Here, we report the application of our recently disclosed hydrosilyl directing group for C-H borylation[9] to alter the inherent selectivity for the reactions of nitrogen heterocycles. This change in selectivity leads to the 7-borylation of indoles lacking any substituent at the 2-position, as well as the borylation of the analogous sites of benzo-fused nitrogen heterocycles containing an N-H bond.



Scheme 49. Borylation of indole at the 7-position with a blocking group at the 2-position

5.3 Results and Discussion

To assess the ability of a hydrosilyl group to affect the selectivity of the borylation of nitrogen heterocycles, we evaluated the borylation of 1-diethylsilylindole with bis-pinacolatodiboron (B_2pin_2) in the presence of the combination of $[Ir(COD)Cl]_2$ and 4,4'-di-*tert*-butylbipyridine (dtbpy).[10] The borylation of this indole derivative occurred with complete selectivity for the borylation at the 7-position in good yield (Equation 5). In contrast, the undirected borylation of indole gives 2- or 2,7-functionalized products depending on the equivalents of the boron reagent (Equation 5). Thus, the hydrosilyl group completely overrides the inherent site-selectivity for the borylation of indole at the 2-position. We envision that this directing effect results from temporary docking of the catalyst on the silyl group by reversible reaction of $[Ir(dtbpy)(Bpin)_3]$ with the Si-H bond to release HBpin and form an intermediate silyl complex. The selectivity for borylation at the 7-position would then result from formation of a five-membered metallacycle from C-H bond cleavage at the 7-position, as shown in Equation 5, versus formation of a four-membered metalacycle from C-H bond cleavage at the 2-position.



With this result in hand, we sought to develop a one-pot protocol for indole borylations by installation of the silyl group, directed borylation, and desilylation. To do so, we first sought conditions for the generation of *N*-hydrosilyl indoles from indole and dihydrosilanes by dehydrogenative coupling under neutral conditions. Studies of several potential catalysts for this reaction showed that [Ru(*p*-cymene)Cl_2]$_2$ formed the *N*-hydrosilyl indole from diethylsilane and indole at room temperature. Indole derivatives that could not be silylated in this fashion were silylated with dimethylchlorosilane and triethylamine as base.

After evaporation of the solvent, the combination of [Ir(cod)Cl]$_2$ and di-*tert*-butyl bipyridine (dtbpy) catalyzed the subsequent borylation of the resulting hydrosilyl indole at the 7-position without interference from the residual ruthenium. Full conversion of the silyl indole occurred after 4 h at 80 °C in the presence of just 0.25% [Ir(cod)Cl]$_2$. Reactions with a catalyst loading of 0.1% [Ir(cod)Cl]$_2$ also occurred in high yield, but a longer reaction time was needed and a second portion of catalyst was often required to achieve full conversion of the silyl indole. Workup with 3 M aqueous NaOAc released the silyl group to give the free 7-borylindole.

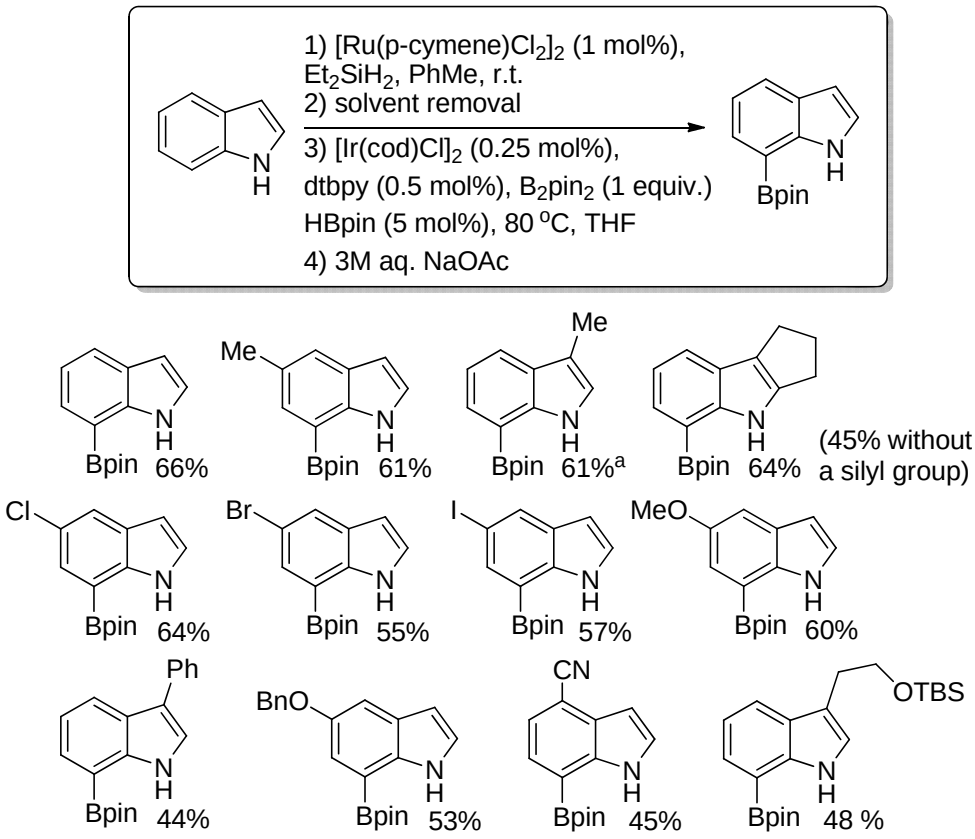


Table 17. Substrate scope of indole borylation at the 7-position

Studies of the scope of the silyl-directed borylation of substituted indoles are summarized in Table 17. The directed borylation reaction tolerates a variety of substituents at the 3-,4-, and 5-positions of the indole framework. Reactions of indoles containing halogens, cyano groups, and alkoxy and benzyloxy groups all occurred to form exclusively the 7-boryl indole, as determined by GC/MS analysis. The isolated yields shown correspond to those for the full reaction sequence starting from the N-H indole.

The borylation of 3-methylindole reveals the striking effect of the *N*-silyl group. Most iridium-catalyzed borylations of arenes with B_2pin_2 are strongly disfavored at positions *ortho* to substituents, but borylations of 3-substituted indoles give 2-boryl indoles in the absence of a directing group. For example, the borylation of 3-

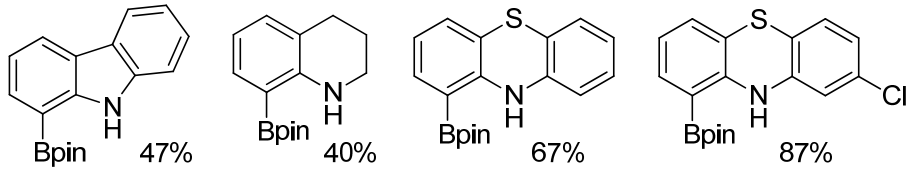
methylindole with B_2pin_2 catalyzed by $[Ir(cod)Cl]_2$ and dtbpy gave a ~2:1 mixture of 2-boryl- and 2,7-diboryl-3-methylindole, whereas the borylation of 3-methyl-*N*-diethylhydrosilylindole occurred exclusively at the 7-position in good yield.

The silyl group also directs borylation exclusively to the indole 7-position in the presence of other aryl C-H bonds. The borylation of 3-phenyl indole forms a mixture of at least three products, whereas the borylation of 3-phenyl-*N*-diethylsilyl indole formed 7-boryl-3-phenylindole without borylation of the phenyl substituent. Moreover, the borylation of *N*-silylindole in a THF solution containing 6 equiv of added benzene led to exclusive borylation of the indole, as assayed by GC-MS. Conversely, the borylation of indole in the presence of 6 equiv of benzene gave a mixture of 2-boryl-indole, 2,7-diboryl-indole and Ph-Bpin.

The hydrosilyl group accelerated not only the rates of the borylation of indoles lacking a 2-substituent, but the rates and yields of the borylations of 2-substituted indoles. The silyl-directed borylation of 1,2,3,4-tetrahydrocyclopentindole occurred at the 7-position in 64% yield for the two-step silylation-borylation process after 8 h, whereas this reaction of indole lacking the silyl group occurred in only 45% yield after a longer 36 h.[7]

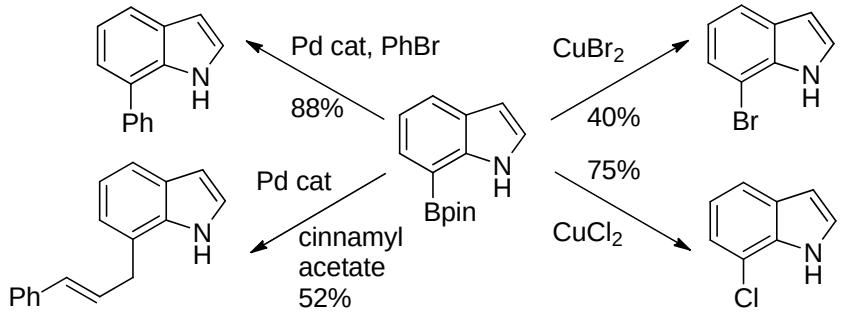
The results of silyl-directed, Ir-catalyzed borylations of other nitrogen heterocycles containing N-H bonds are shown in Scheme 50. The borylation of carbazole, phenothiazines, and tetrahydroquinoline occurred to full conversion and in moderate to good yield in the presence of 1 mol % $[Ir(cod)OMe]_2$ and 2 mol % dtbpy. The lower yields observed in some cases were due to protodeborylation during cleavage of the silyl group. The borylation of 2-chlorophenothiazine underwent selective borylation at the less hindered *ortho*-C-H bond. Phenothiazine is the core of a number of neuroleptic

antipsychotic drugs, including chlorpromazine, fluphenazine, and prochlorperazine, and is contained within components of organic solar cells and photovoltaics.[11]



Scheme 50. Ir-catalyzed, silyl-directed borylation of other nitrogen-containing heterocycles

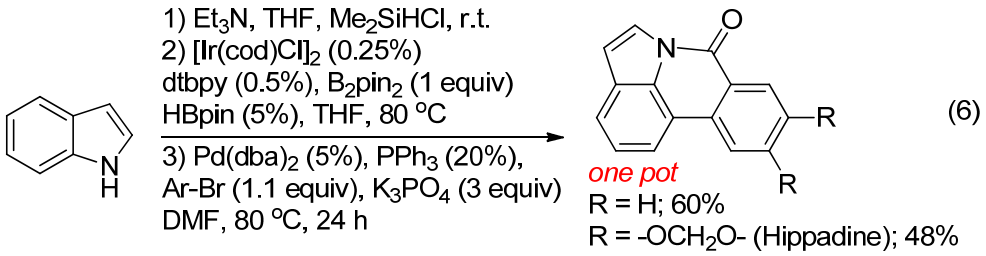
The conversion of 7-boryl indole to further functionalized materials is shown in Scheme 51. Suzuki-Miyaura coupling with bromobenzene in the presence of catalytic $Pd(dba)_2$ and PPh_3 and K_3PO_4 as base in DMF at 80 °C gave 7-phenylindole. Palladium-catalyzed allylation with $PdCl_2$, tri-2-furylphosphine, cinnamyl acetate and KF in MeOH gave 7-cinnamylindole.[12] Halogenation using the protocol developed for the conversion of arylboronates gave 7-bromo- and 7-chloroindole.[13]



Scheme 51. Functionalization of 7-borylindoles into other useful indole building blocks

To further illustrate the potential of the silyl-directed, Ir-catalyzed borylation of indoles to facilitate the synthesis of biologically active compounds, we prepared the core of the pyrrolophenanthridone natural products that have shown promising antitumor and other biological activity. Previous syntheses of this class of natural products have utilized pre-functionalized starting materials,[14] such as 7-bromoindole,[15] and relied on blocking

groups at the C-2 position,[8] and typically required several steps or harsh reaction conditions. In contrast, the Ir-catalyzed, silyl-directed, 7-borylation of indole, followed by Suzuki-Miyaura coupling of the desired *ortho*-bromobenzoate and lactamization in situ gave the pyrrolophenanthridone alkaloid core and the natural product Hippadine in a single, one-pot sequence in good yield (Equation 6). Because this approach begins with an indole, and a benzoate, this method should allow the modular introduction of groups on both the indole and arene units.



(6)

5.4 Conclusion and Outlook

In conclusion, a highly selective method has been developed for the Ir-catalyzed, silyl-directed C-H borylation of nitrogen heterocycles, including a general borylation of indole at the 7-position. This transformation occurs with a low catalyst loading in short reaction times under mild conditions. Furthermore, this reaction possess good functional group tolerance, can be extended to the directed borylation of other nitrogen-containing heterocycles, and creates a versatile intermediate for further functionalization. Studies on the origin of the regioselectivity and application of this approach to additional directed functionalizations are in progress.

5.5 Experimental Information

General Procedures. All reactions were conducted under an argon or nitrogen atmosphere in flame-dried glassware or in an Innovative Technologies drybox. Dry and

degassed solvents were used unless otherwise noted. Column chromatography was performed using Silicycle silica gel. Analytical thin-layer chromatography was performed on glass plates coated with silica gel (Silicycle, 60 A pore size, 40-64 um particle size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by ultraviolet light and staining solution of *p*-anisaldehyde or $KMNO_4$.

Materials. $[Ru(p\text{-cymene})Cl_2]_2$ was obtained from Strem Chemicals and used as received. $[Ir(cod)Cl]_2$ and $[Ir(cod)OMe]_2$ were obtained from Johnson Matthey and used as received. 4,4'-di-*tert*-butylbipyridine was obtained from Aldrich Chemicals and used as received. B_2pin_2 was obtained from Allychem and used as received. HBpin was obtained from Aldrich Chemicals and distilled before use. Et_2SiH_2 was obtained from Aldrich Chemicals or Alfa Aesar and used as received. Et_3N was obtained from Fisher Scientific and used as received. Dimethylchlorosilane was obtained from Gelest and used as received. NaH was obtained as a 60% suspension in mineral oil and washed with pentane and dried before use. All indoles and nitrogen heterocycles were obtained from Aldrich Chemicals, Alfa Aesar, TCI America or Acros and used as received. $Pd(dba)_2$ was prepared using standard methods. Bromobenzene, cinnamyl acetate, PPh_3, K_3PO_4, $CuCl_2$, $CuBr_2$ and methyl 2-bromobenzoate were obtained from Aldrich and used as received. KF was obtained from Acros and used as received. Methyl 6-bromo-1,3-benzodioxole-5-carboxylate was prepared from 6-bromopiperonal (purchased from Aldrich) using the method of McDonald, et. Al: McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213.

Instruments. ^1H NMR spectra were recorded on a 500 MHz Varian instrument (126 MHz for ^{13}C). ^{11}B NMR spectra were recorded on a 300 MHz Varian instrument.

Chemical shifts are reported in parts per million relative to residual protiated solvent (7.26 ppm for $CDCl_3$ and 7.15 for C_6D_6). In general, the carbon bonded to boron the heterocycle borylation products could not be observed via ^{13}C NMR spectroscopy. This is consistent with previous reports of 7-borylindole compounds. GC-MS data were obtained on an Agilient 6890-N GC system containing an Alltech EC-1 capillary column and an Agilient 5973 mass selective detector. Elemental analyses were conducted by the University of Illinois at Urbana-Champaign Microanalysis Laboratory or Robertson Microlit Laboratories (Madison, NJ, USA).

General procedures for the silyl-directed borylation of indoles.

Borylation of *N*-diethylsilylindoles (Procedure 1)

Inside a glove box, $[Ru(p\text{-cymene})Cl_2]_2$ (6.0 mg, 0.01 mmol, 0.01 equiv), the indole (1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred for 2-12 h until GC analysis showed full conversion of the indole to the *N*-silylindole. The volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. GC analysis indicated full conversion of the *N*-diethylsilylindole after 4-16 h. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4-6 h. Upon complete desilylation, as assayed by GC, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated

and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography eluting under the conditions described below for each example afforded pure product.

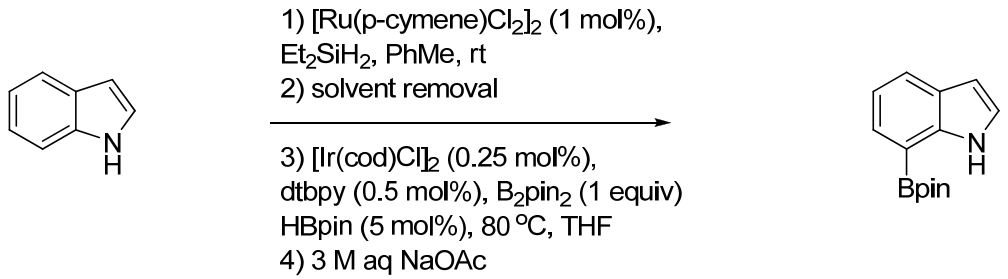
Borylation of *N*-dimethylsilylindoles (Procedure 2)

Inside a glove box, triethylamine (160 mg, 1.50 mmol, 1.50 equiv), the indole (1.00 mmol, 1.00 equiv), dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 4-6 h until GC analysis showed full conversion of the indole to the *N*-silylindole. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. GC analysis indicated full conversion of the *N*-dimethylsilylindole after 4-16 h. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 1 mL of saturated $NaHCO_3$ (aq) was added. The mixture was stirred at room temperature for 6 h. Upon complete desilylation as assayed using GC analysis, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography, eluting under the conditions described below for each example, afforded pure product.

Borylation of *N*-diethylsilylindoles without use of a glovebox (Procedure 3)

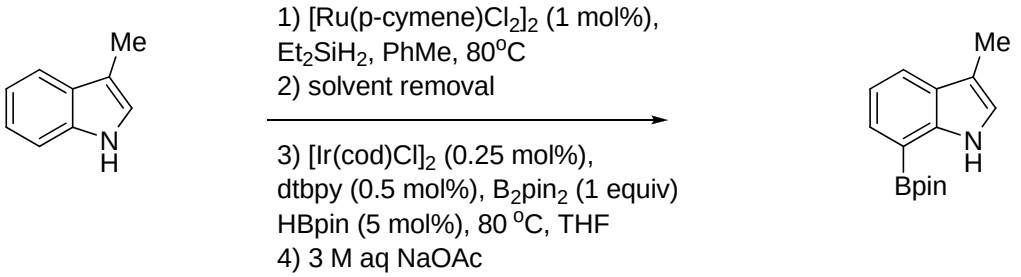
$[Ru(p\text{-cymene})Cl_2]_2$ (6.0 mg, 0.010 mmol, 0.010 equiv) and the indole (1.00 mmol, 1.00 equiv) were added to a dry glass reaction vessel equipped with a side arm and a vacuum valve and sealed under N_2. The vessel was evacuated and filled with N_2 three times. Under a positive flow of N_2, a mixture of diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added. The vessel was sealed and stirred.for 2-12 h until GC analysis showed full conversion of the indole to the *N*-silylindole. The volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv) were added to the vessel. The vessel was evacuated and refilled with N_2 three times. Under a positive flow of N_2, a mixture of HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) was added to the reaction mixture. The vessel was sealed and the reaction mixture was heated at 80 °C. GC analysis indicated full conversion of the *N*-diethylsilylindole after 4-16 h. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4-6 h. Upon complete desilylation, as assayed by GC, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography eluting under the conditions described below for each example afforded pure product.

Specific Experimental Procedures for the Borylation of Indoles



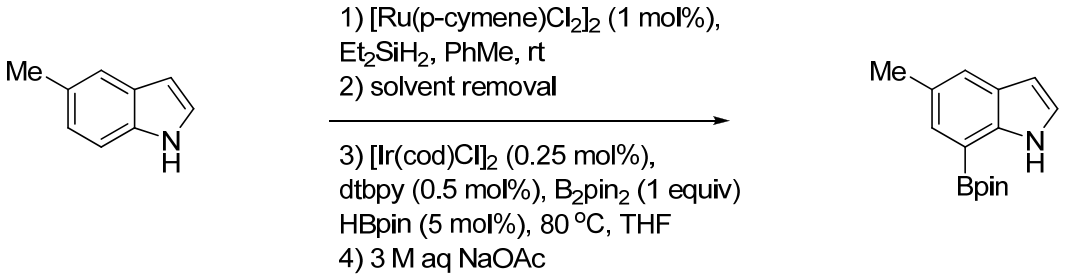
Borylation of indole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), indole (117 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at room temperature for 2 h, at which time, GC analysis showed full conversion of the indole to the *N*-silylindole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.005 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 4 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 6 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (85:15 hexanes:ethyl acetate) afforded the known product[2] judged to be pure by NMR spectroscopy (160 mg, 66%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.80 (d, J = 7.9, 1H), 7.68 (d, J = 7.0, 1H), 7.29 (t, J = 2.7, 1H), 7.16 (t, J = 7.4, 1H), 6.57 (m, 1H),

1.42 (s, 12H). ^{13}C NMR (126 MHz, CDCl3) δ 141.20, 129.47, 127.02, 124.50, 124.30, 119.55, 102.20, 83.95, 25.25. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.3.



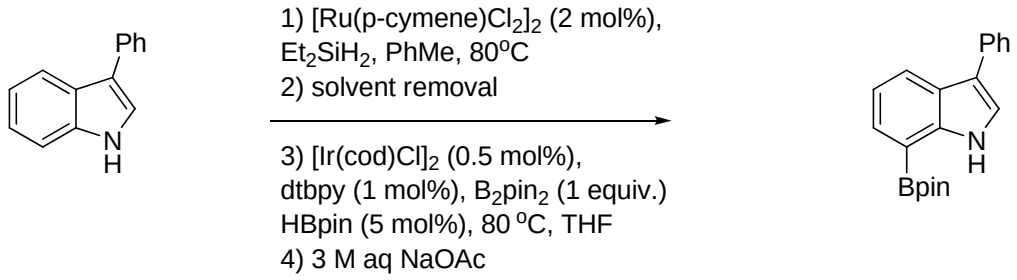
Borylation of 3-methylindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), 3-methylindole (131 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 80 °C for 12 h, at which time GC analysis showed full conversion of the indole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 6 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 6 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (156 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 1H),

7.74 (d, J = 7.8, 1H), 7.68 (dd, J = 0.9, 7.1, 1H), 7.17 (dd, J = 7.1, 7.8, 1H), 7.05 (d, J = 0.9, 1H), 2.38 (s, 3H), 1.42 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.68, 129.34, 127.43, 122.61, 121.75, 118.78, 111.28, 83.96, 25.25, 9.93. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.6. Anal Calcd. for $C_{15}H_{20}BNO_2$: C, 70.0; H, 7.84; N, 5.45; found: C, 69.6; H, 7.96; N, 5.48.



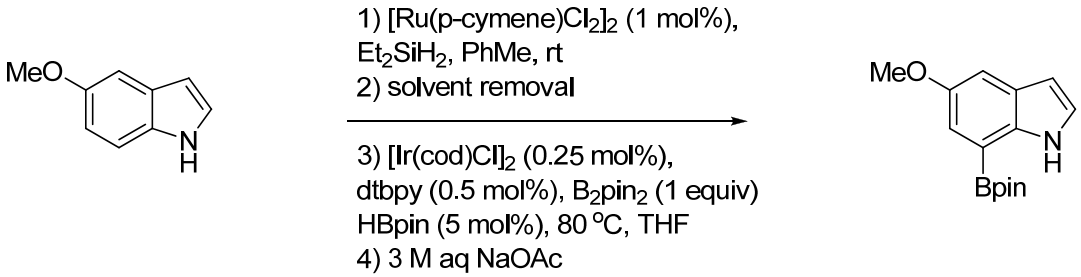
Borylation of 5-methylindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), 5-methylindole (131 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 80 °C for. After 12 h, at which time, GC analysis indicated that the indole was fully conversion of the indole to *N*-diethylsilylindole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 4 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated

and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (156 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.64 (s, 1H), 7.58 (s, 1H), 7.28 (t, J = 2.7, 1H), 6.54 (d, J = 2.7, 1H), 2.53 (s, 3H), 1.46 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.69, 130.87, 128.59, 127.47, 124.47, 124.41, 101.71, 84.06, 25.28, 21.56. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.8. Anal Calcd. for $C_{15}H_{20}BNO_2$: C, 70.0; H, 7.84; N, 5.45; found: C, 70.2; H, 8.02; N, 5.49.



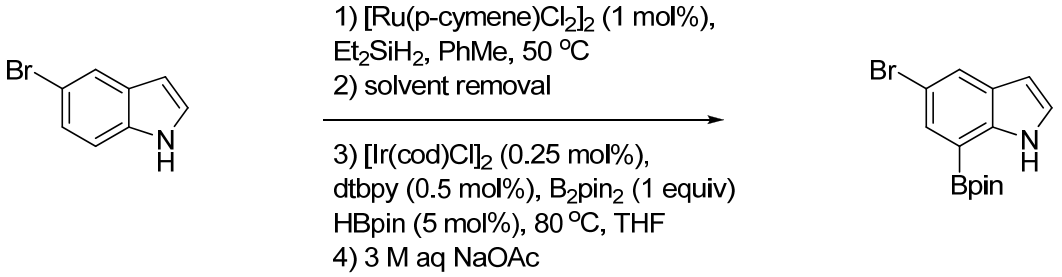
Borylation of 3-phenylindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (12 mg, 0.020 mmol, 0.020 equiv), 3-phenylindole (197 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 80 °C for 16 h, at which time GC-MS analysis showed full conversion of 3-phenylindole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (3.4 mg, 0.0050 mmol, 0.050 equiv), dtbpy (2.7 mg, 0.010 mmol, 0.010 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (2.0 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 12 h, GC-MS analysis indicated full conversion of the *N*-diethylsilyl-3-phenylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2

mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (140 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.13 (d, J = 8.0, 1H), 7.77 (d, J = 7.0, 1H), 7.73 (d, J = 7.5, 2H), 7.49 (m, 3H), 7.33 (t, J = 7.4, 1H), 7.27 (t, J = 7.5, 1H), 1.45 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.11, 136.09, 129.93, 129.02, 127.76, 126.09, 124.97, 123.64, 122.04, 120.09, 118.06, 84.18, 25.28. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.6. Anal Calcd. for $C_{20}H_{22}BNO_2$: C, 75.25; H, 6.95; N, 4.39; found: C, 75.29; H, 6.70; N, 4.16.



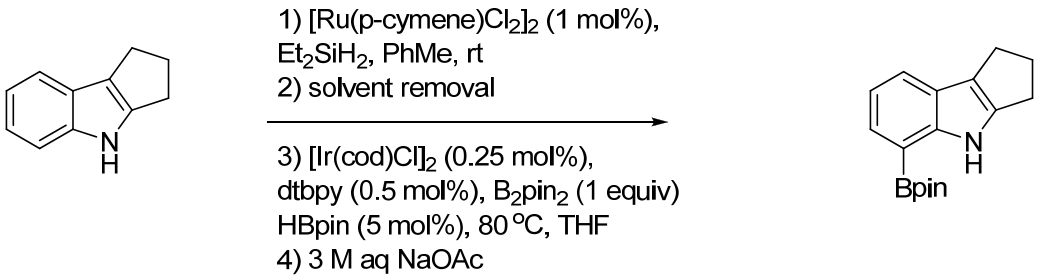
Borylation of 5-methoxyindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), 5-methoxyindole (148 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at room temperature for 6 h, at which time GC analysis showed full conversion of the indole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at

80 °C. After 6 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (85:15 hexanes:ethyl acetate) afforded analytically pure product (160 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.36 (d, J = 2.4, 1H), 7.31 (d, J = 2.3, 1H), 7.28 (t, J = 2.7, 1H), 6.51 (dd, J = 2.3, 2.9, 1H), 3.90 (s, 3H), 1.42 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.03, 136.72, 127.87, 125.17, 118.05, 107.81, 101.77, 84.17, 56.48, 25.24. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.8. Anal Calcd. for $C_{15}H_{20}BNO_3$: C, 65.96; H, 7.38; N, 5.13; found: C, 65.70; H, 7.63; N, 4.95.



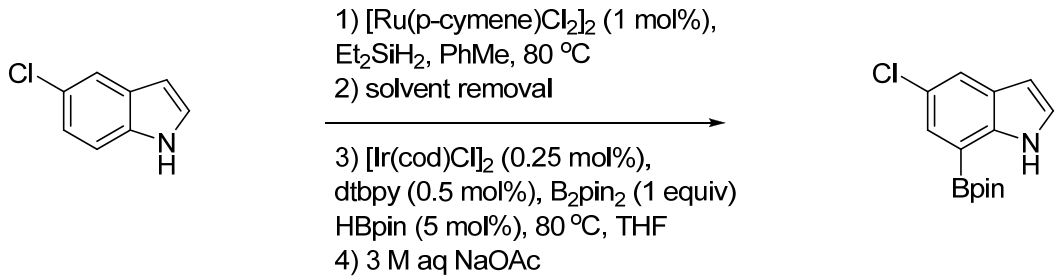
Borylation of 5-bromoindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), 5-bromoindole (197 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 50 °C for 12 h, at which time GC analysis showed full conversion of the indole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025

mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 6 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (85:15 hexanes:ethyl acetate) afforded analytically pure product (175 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.88 (d, J = 1.7, 1H), 7.73 (d, J = 1.8, 1H), 7.27 (m, 1H), 6.49 (m, 1H), 1.40 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.74, 131.61, 129.00, 126.66, 125.55, 113.15, 101.82, 84.43, 25.22. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.8. Anal Calcd. for $C_{14}H_{17}BBrNO_2$: C, 52.22; H, 5.32; N, 4.35; found: C, 52.16; H, 5.52; N, 3.96.

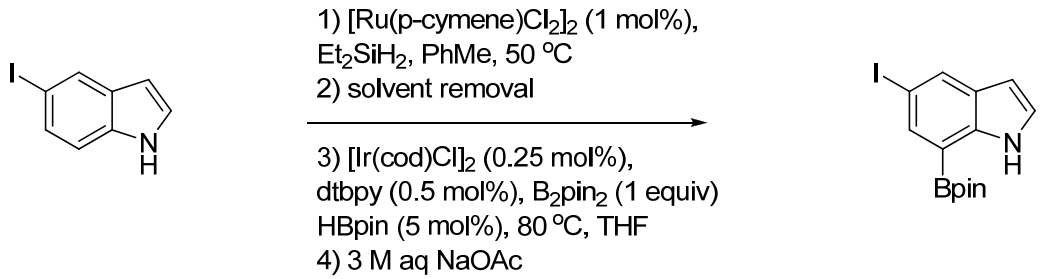


Borylation of 1,2,3,4-Tetrahydrocyclopentindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), 1,2,3,4-Tetrahydrocyclopentindole (158 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and

toluene (0.5 mL) were added to a dry vial. The mixture was stirred at room temperature for 6 h, at which time GC analysis showed full conversion of the indole. The volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 8 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded the known product[2] judged to be pure by NMR spectroscopy (179 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.63 (d, J = 2.4, 1H), 7.62 (d, J = 1.3, 1H), 7.16 (t, J = 7.4, 1H), 2.98 (t, J = 7.1, 2H), 2.90 (t, J = 6.9, 2H), 2.60 (m, 2H), 1.45 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.64, 144.00, 127.86, 123.93, 122.22, 119.30, 119.12, 84.00, 29.06, 26.32, 25.27, 24.75. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.8.

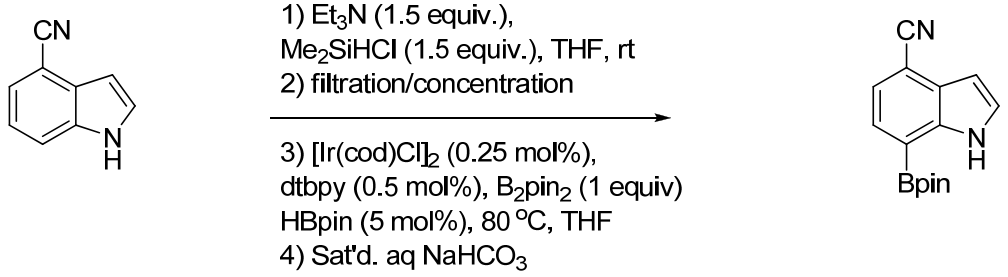


Borylation of 5-chloroindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol), 5-chloroindole (151 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 80 °C for 2 h, at which time GC-MS analysis showed full conversion of 5-chloroindole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 4 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (176 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.74 (d, J = 1.8, 1H), 7.63 (d, J = 1.9, 1H), 7.30 (m, 1H), 6.51 (m, 1H), 1.41 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.55, 129.08, 128.40, 125.75, 125.48, 123.62, 101.92, 84.44, 25.23. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.4. Anal Calcd. for $C_{14}H_{17}BClNO_2$: C, 60.58; H, 6.17; N, 5.05; found: C, 60.53; H, 6.32; N, 4.97.



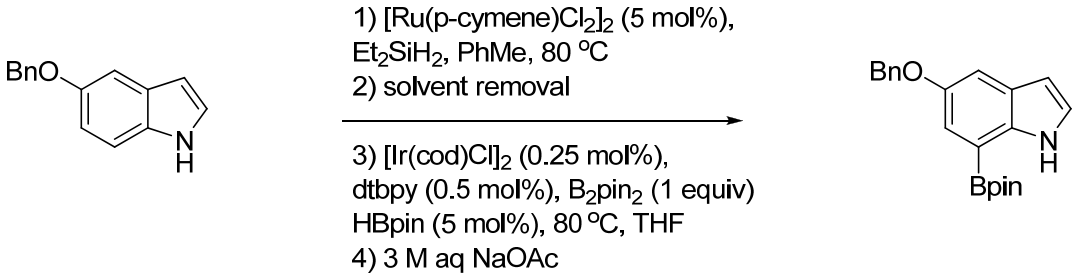
Borylation of 5-iodoindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (12.0 mg, 0.020 mmol, 0.020 equiv), 5-iodoindole (243 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 50 °C for 2 h, at which time GC-MS analysis showed full conversion of 5-chloroindole. The volatile materials were removed under vacuum. . [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 4 h, GC analysis indicated full conversion of the *N*-diethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of an aqueous solution of 3 M NaOAc was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (210 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.12 (s, 1H), 7.93 (d, J = 1.5, 1H), 7.24 (m, 1H), 6.49 (m, 1H), 1.41 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.15, 137.11, 132.90, 129.83,

129.48, 125.24, 101.59, 84.45, 25.25. ^{11}B NMR (300MHz, $CDCl_3$): δ 32.5. Anal Calcd. for $C_{14}H_{17}BINO_2$: C, 45.57; H, 4.64; N, 3.80; found: C, 45.28; H, 4.44; N, 3.88.



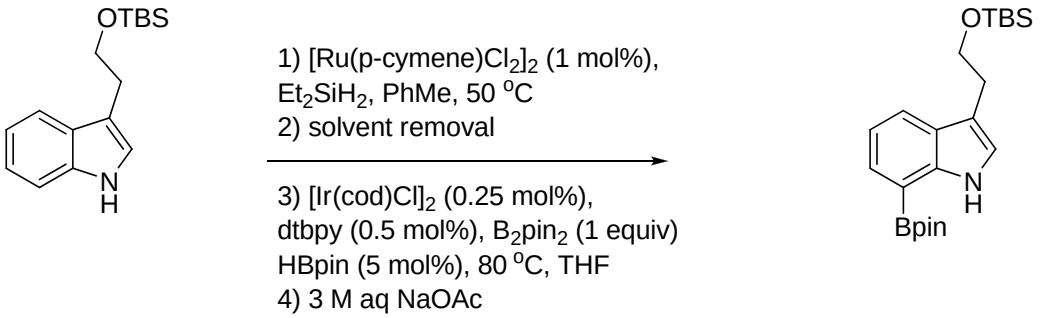
Borylation of 4-cyanoindole. Inside a glove box, triethylamine (160 mg, 1.50 mmol, 1.50 equiv), 4-cyanoindole (142 mg, 1.00 mmol, 1.00 equiv), dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 6 h, at which time GC analysis showed full conversion of the indole. The reaction mixture was filtered through Celite and the volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 16 h, GC analysis indicated full conversion of the *N*-dimethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 1 mL of saturated $NaHCO_3$ (aq) was added. The mixture was stirred at room temperature for 6 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (75:25 hexanes:ethyl acetate) afforded analytically pure product

(120 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.65 (d, J = 7.3, 1H), 7.46 (d, J = 7.3, 1H), 7.44 (t, J = 2.7, 1H), 6.76 (m, 1H), 1.41 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.86, 128.47, 128.27, 127.12, 124.45, 119.03, 105.81, 101.28, 84.77, 25.22. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.9. Anal Calcd. for $C_{15}H_{17}BN_2O_2$: C, 67.19; H, 6.39; N, 10.45; found: C, 67.14; H, 6.37; N, 10.05



Borylation of 5-benzyloxylindole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (30 mg, 0.050 mmol, 0.05 equiv), 5-benzyloxyindole (223 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 80 °C for 12 h, at which time GC-MS analysis showed full conversion of 5-benzyloxyindole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1.0 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 6 h, GC-MS analysis indicated full conversion of the *N*-diethylsilyl-5-benzyloxyindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated

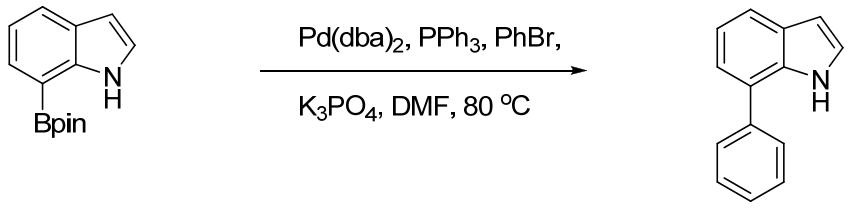
and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (183 mg, 53%). ^{1}H NMR (500 MHz, CDCl3) δ 9.14 (s, 1H), 7.51 (d, J = 7.5, 3H), 7.47 (d, J = 2.4, 1H), 7.41 (t, J = 7.5, 3H), 7.37 (d, J = 2.4, 1H), 7.35 (d, J = 7.3, 1H), 7.27 (t, J = 2.7, 1H), 6.50 (dd, J = 2.3, 3.0, 1H), 5.16 (s, 2H), 1.42 (s, 12H). ^{13}C NMR (126 MHz, CDCl3) δ 153.22, 138.16, 136.85, 128.76, 127.87, 127.81, 127.70, 125.14, 119.20, 109.20, 101.88, 84.31, 71.42, 25.26. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.6. Anal Calcd. for $C_{21}H_{24}BNO_3$: C, 72.2; H, 6.9; N, 4.0; found: C, 72.0; H, 6.5; N, 3.7.



Borylation of 3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indole. Inside a glove box, [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.010 mmol, 0.010 equiv), 3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indole (275 mg, 1.00 mmol, 1.00 equiv), diethylsilane (132 mg, 1.50 mmol, 1.50 equiv) and toluene (0.5 mL) were added to a dry vial. The mixture was stirred at 50 °C for 12 h, at which time GC-MS analysis showed full conversion of 3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indole. The volatile materials were removed under vacuum. [Ir(cod)Cl]$_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1.0 mL) were added to the vial, and the reaction mixture was heated at 80 °C. After 6 h, GC-MS analysis indicated full conversion of the *N*-

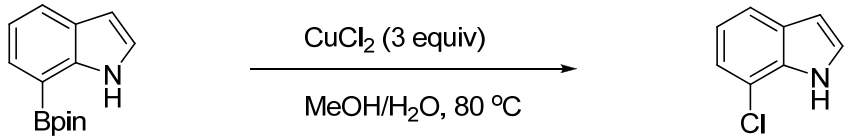
diethylsilyl-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 0.5 mL of 3 M NaOAc (aq) was added. The mixture was stirred at room temperature for 4 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (193 mg, 48%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.80 (d, J = 7.8, 1H), 7.71 (d, J = 6.9, 1H), 7.19 (t, J = 7.4, 1H), 7.15 (s, 1H), 3.94 (t, J = 7.4, 2H), 3.07 (t, J = 7.4, 2H), 1.44 (s, 12H), 0.98 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.58, 129.44, 126.93, 122.72, 122.24, 118.97, 112.82, 84.00, 64.38, 29.37, 26.30, 25.26, 18.67, -4.96. ^{11}B NMR (300MHz, $CDCl_3$): δ 32.5. Anal Calcd. for $C_{16}H_{20}BNO_4$: C, 65.82; H, 9.04; N, 3.49; found: C, 65.86; H, 9.18; N, 3.47.

Specific Experimental Procedures for Functionalization of 7-borylindoles

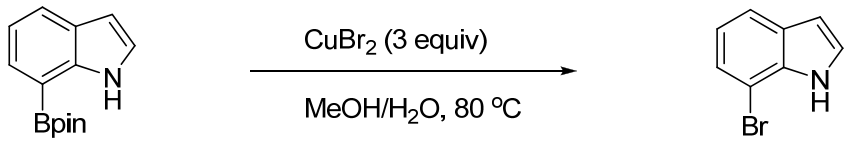


Suzuki-Miyaura Coupling of 7-borylindole with bromobenzene. 7-borylindole (243 mg, 1.00 mmol, 1.00 equiv), $Pd(dba)_2$ (28.8 mg, 0.050 mmol, 0.050 equiv), PPh_3 (52.4 mg, 0.200 mmol, 0.200 equiv), K_3PO_4 (640 mg, 3.00 mmol, 3.00 equiv), bromobenzene (220 mg, 1.40 mmol, 1.40 equiv) and DMF (4 mL) were added to a dry vial. The

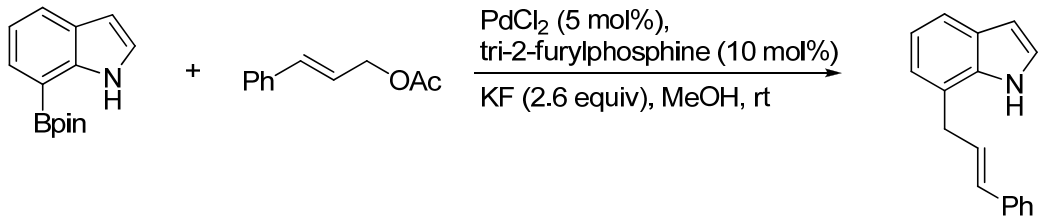
reaction mixture was heated at 80 °C for 10 h. The reaction mixture was cooled to room temperature, filtered through Celite, washing with Et_2O. The filtrate was concentrated. Column chromatography (80:20 hexanes:ethyl acetate) afforded the known product judged to be pure by NMR spectroscopy (169 mg, 88%). ^{1}H NMR (499 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.77 (dd, J = 4.1, 4.7, 1H), 7.73 (d, J = 8.2, 2H), 7.60 (t, J = 7.6, 2H), 7.51 (t, J = 7.4, 1H), 7.34 (t, J = 5.0, 2H), 7.21 (d, J = 2.0, 1H), 6.73 (d, J = 4.3, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.64, 134.05, 129.47, 128.66, 128.54, 127.73, 125.97, 124.81, 122.23, 120.64, 120.39, 103.31.



Chlorination of 7-borylindole. 7-borylindole (243 mg, 1.00 mmol, 1.00 equiv) was dissolved in MeOH (12 mL). $CuCl_2$ (404 mg, 3.00 mmol, 3.00 equiv) was dissolved in H_2O (12 mL). The aqueous $CuCl_2$ solution was added to the MeOH solution, and the mixture was heated at 80 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (80:20 hexanes:ethyl acetate) afforded the known product judged to be pure by NMR spectroscopy (113 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.56 (d, J = 7.9, 1H), 7.26 (d, J = 2.5, 1H), 7.21 (d, J = 7.6, 1H), 7.07 (t, J = 7.8, 1H), 6.61 (d, J = 4.3, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.38, 129.54, 124.98, 121.56, 120.81, 119.58, 116.81, 103.92.



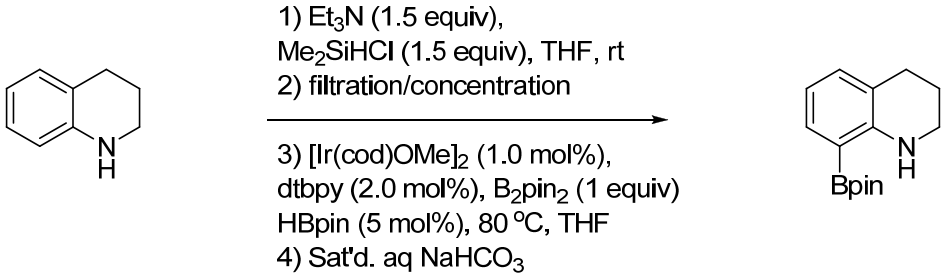
Bromination of 7-borylindole. 7-borylindole (243 mg, 1.00 mmol, 1.00 equiv) was dissolved in MeOH (12 mL). $CuBr_2$ (670 mg, 3.00 mmol, 3.00 equiv) was dissolved in H_2O (12 mL). The aqueous $CuBr_2$ solution was added to the MeOH solution and the mixture was heated at 80 °C for 4 h. The reactions mixture was cooled to room temperature and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (80:20 hexanes:ethyl acetate) afforded the known product judged to be pure by NMR spectroscopy (78 mg, 40%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.63 (d, J = 7.9, 1H), 7.40 (d, J = 7.6, 1H), 7.26 (m, 1H), 7.05 (t, J = 7.7, 1H), 6.70 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.84, 129.26, 124.96, 124.59, 121.26, 120.22, 104.91, 104.11.



Allylation of 7-borylindole. $PdCl_2$ (7.0 mg, 0.039 mmol, 0.05 equiv), tri-2-furylphosphine (18 mg, 0.078 mmol, 0.10 equiv), 7-borylindole (243 mg, 1.00 mmol, 1.30 equiv), cinnamyl acetate (136 mg, 0.770 mmol, 1.00 equiv), KF (118 mg, 2.00 mmol, 2.6 equiv), and MeOH (4 mL) were added to a dry vial. The reaction was stirred at room temperature. After 24 h, GC analysis indicated full consumption of cinnamyl acetate. The reaction mixture was diluted with EtOAc and filtered through silica gel. The reaction mixture was concentrated under vacuum. Column chromatography (95:5

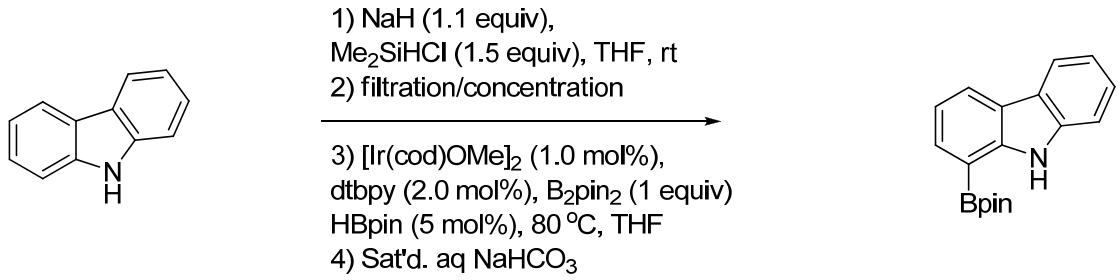
hexanes:ethyl acetate) afforded analytically pure product (121 mg, 52%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.67 (d, J = 7.7, 1H), 7.43 (d, J = 7.7, 2H), 7.38 (t, J = 7.6, 2H), 7.31 (t, J = 7.2, 1H), 7.18 (dt, J = 7.3, 17.1, 3H), 6.66 (dd, J = 6.2, 9.4, 2H), 6.58 – 6.45 (m, 1H), 3.86 (d, J = 6.5, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.32, 135.47, 131.61, 128.91, 128.65, 128.29, 127.69, 126.48, 124.42, 122.51, 122.44, 120.34, 119.58, 103.16, 36.19. Anal Calcd. for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00; found: C, 87.27; H, 6.28; N, 5.93.

Specific Experimental Procedures for Borylation of other Nitrogen-Containing Heterocycles



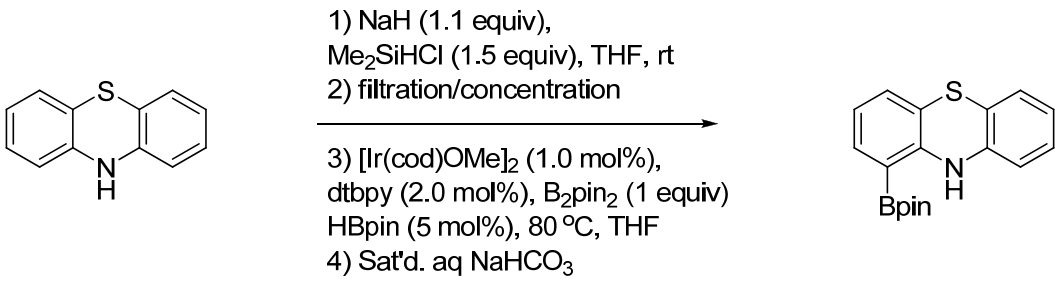
Borylation of 1,2,3,4-tetrahydroquinoline. Inside a glove box, triethylamine (160 mg, 1.50 mmol, 1.50 equiv), 1,2,3,4-tetrahydroquinoline (133 mg, 1.00 mmol, 1.00 equiv), dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 6 h, at which time GC analysis showed full conversion of the 1,2,3,4-tetrahydroquinoline. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. $[Ir(cod)OMe]_2$ (6.8 mg, 0.010 mmol, 0.010 equiv), dtbpy (5.6 mg, 0.020 mmol, 0.020 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. GC analysis indicated full conversion of the *N*-dimethylsilyltetrahydroquinoline. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 1 mL of saturated $NaHCO_3$ (aq) was added. The mixture was stirred at room temperature for 6 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography

(90:10 hexanes:ethyl acetate) afforded analytically pure product (64 mg, 40%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.44 (d, J = 7.4, 1H), 6.99 (d, J = 7.2, 1H), 6.50 (t, J = 7.3, 1H), 5.84 (s, 1H), 3.36 (m, 2H), 2.75 (t, J = 6.4, 2H), 1.91 (m, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.58, 135.15, 133.08, 120.46, 115.11, 83.58, 41.81, 27.79, 25.11, 21.80. ^{11}B NMR (300MHz, $CDCl_3$): δ 33.3. Anal Calcd. for $C_{15}H_{22}BNO_2$: C, 69.52; H, 8.56; N, 5.40; found: C, 69.50; H, 8.68; N, 5.13.



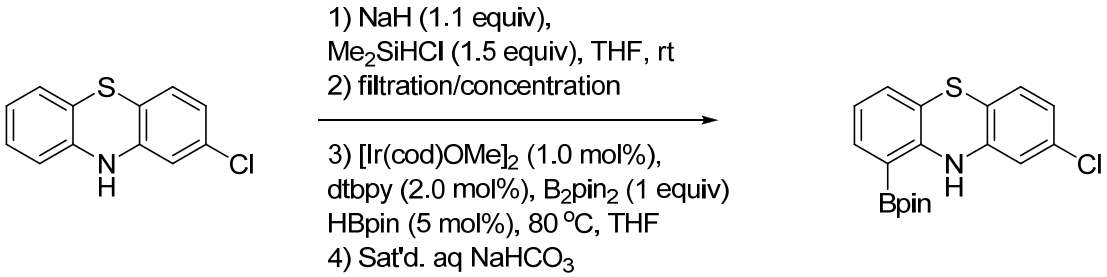
Borylation of carbazole. Inside a glove box, carbazole (168 mg, 1.00 mmol, 1.00 equiv), NaH (27 mg, 1.1 mmol, 1.1 equiv), and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 2 h. Dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) was added. The mixture was stirred at room temperature for 10 h, at which time GC analysis showed full conversion of the carbazole. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. $[Ir(cod)OMe]_2$ (6.8 mg, 0.010 mmol, 0.010 equiv), dtbpy (5.6 mg, 0.020 mmol, 0.020 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial, and the reaction mixture was heated at 80 °C. GC analysis indicated full conversion of the *N*-dimethylsilylcarbazole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 1 mL of saturated $NaHCO_3$ (aq) was added. The mixture

was stirred at room temperature for 6 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (138 mg, 47%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.23 (d, J = 7.5, 1H), 8.12 (t, J = 7.0, 2H), 7.91 (d, J = 7.0, 1H), 7.55 (d, J = 8.0, 1H), 7.50 – 7.37 (m, 2H), 7.28 (dd, J = 7.3, 14.7, 3H), 1.47 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.30, 139.57, 133.08, 125.98, 123.94, 123.14, 122.53, 120.54, 119.39, 118.98, 110.82, 84.27, 25.30. Anal Calcd. for $C_{18}H_{20}BNO_2$: C, 73.74; H, 6.88; N, 4.78; found: C, 73.66; H, 7.10; N, 4.78.



Borylation of phenothiazine. Inside a glove box, phenothiazine (199 mg, 1.00 mmol, 1.00 equiv), NaH (27 mg, 1.1 mmol, 1.1 equiv), and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 2 h. Dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) was added, and the mixture was stirred at room temperature for 10 h. The reaction mixture was filtered and concentrated, washing with Et_2O. $[Ir(cod)OMe]_2$ (6.8 mg, 0.010 mmol, 0.010 equiv), dtbpy (5.6 mg, 0.020 mmol, 0.020 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial.. The reaction mixture was heated at 80 °C for 24 h, at which time GC analysis indicated full conversion of the *N*-

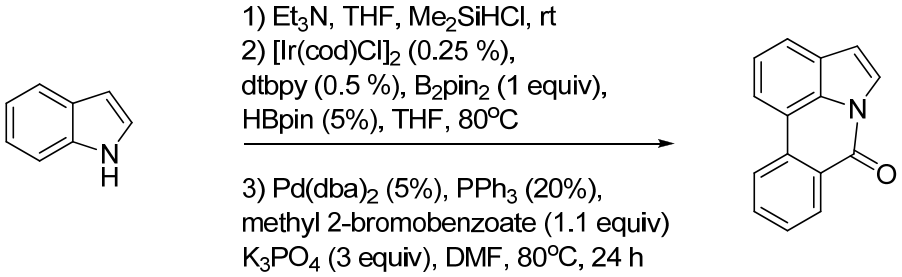
dimethylsilyl-phenothiazine. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (208 mg, 64%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.48 (d, 1H), 7.09 (d, J = 7.5, 1H), 7.01 (m, 2H), 6.82 (ddd, J = 4.6, 9.1, 10.5, 2H), 6.58 (d, J = 7.8, 1H), 1.41 (s, J = 1.6, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.95, 142.23, 135.02, 130.42, 127.49, 126.86, 122.71, 121.72, 118.55, 118.27, 115.01, 84.48, 25.21. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.7. Anal Calcd. for $C_{18}H_{20}BNO_2S$: C, 66.47; H, 6.20; N, 4.31; found: C, 66.22; H, 6.19; N, 4.38.



Borylation of 2-chlorophenothiazine. Inside a glove box, 2-chlorophenothiazine (234 mg, 1.00 mmol, 1.00 equiv), NaH (27 mg, 1.1 mmol, 1.1 equiv), and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 2 h. Dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) was added, and the mixture was stirred at room temperature for 10 h. The reaction mixture was filtered and concentrated, washing with Et_2O. $[Ir(cod)OMe]_2$ (6.8 mg, 0.010 mmol, 0.010 equiv), dtbpy (5.6 mg, 0.020 mmol, 0.020 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial.. The reaction mixture was heated at 80 °C for 24 h, at which time GC analysis indicated full conversion of the *N*-dimethylsilyl-2-chlorophenothiazine. The reaction mixture was cooled to room

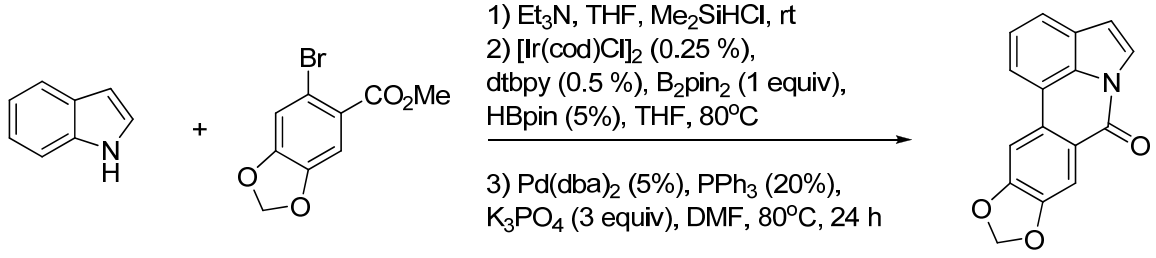
temperature. The volatile materials were removed from the reaction mixture under high vacuum at 40 °C. The reaction mixture was dissolved in 2 mL of THF, and 1 mL of saturated $NaHCO_3$ (aq) was added. The mixture was stirred at room temperature for 6 h. Upon complete desilylation, the reaction mixture was diluted with Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (90:10 hexanes:ethyl acetate) afforded analytically pure product (314 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.46 (dd, J = 1.2, 7.4, 1H), 7.04 (d, J = 8.4, 1H), 6.80 (m, 3H), 6.50 (d, J = 1.9, 1H), 1.39 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.04, 143.30, 135.15, 132.96, 130.39, 127.47, 122.41, 122.21, 117.86, 117.11, 114.81, 84.64, 25.19. ^{11}B NMR (300MHz, $CDCl_3$): δ 31.8. Anal Calcd. for $C_{18}H_{19}BNO_2SCl$: C, 60.11; H, 5.632 N, 3.89 found: C, 60.34; H, 5.49; N, 4.10.

Specific Experimental Procedures for Synthesis of Pyrrolophenanthridone Alkaloids



Synthesis of core of pyrrolophenanthridone alkaloids. Inside a glove box, triethylamine (160 mg, 1.50 mmol, 1.50 equiv), indole (117 mg, 1.00 mmol, 1.00 equiv), dimethylchlorosilane (144 mg, 1.50 mmol, 1.50 equiv) and THF (2 mL) were added to a dry vial. The mixture was stirred at room temperature for 6 h, at which time GC analysis

showed full conversion of the indole. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.0025 equiv), dtbpy (1.4 mg, 0.0050 mmol, 0.0050 equiv), B_2pin_2 (254 mg, 1.00 mmol, 1.00 equiv), HBpin (0.008 mL, 0.05 mmol, 0.05 equiv), and THF (1 mL) were added to the vial.. The reaction mixture was heated at 80 °C for 6 h, at which time GC analysis indicated full conversion of the *N*-dimethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum. $Pd(dba)_2$ (30 mg, 0.050 mmol, 0.050 equiv), PPh_3 (52 mg, 0.20 mmol, 0.20 equiv), methyl 2-bromobenzoate (255 mg, 1.20 mmol, 1.20 equiv), K_3PO_4 (638 mg, 3.00 mmol, 3.00 equiv) and DMF (4 mL) were added to the reaction mixture. The reaction mixture was heated to 80 ^oC for 24 h. The reaction was filtered through Celite, washed with EtOAc, and concentrated under vacuum. Column chromatography (80:20 hexanes:ethyl acetate) afforded the known product judged to be pure by NMR spectroscopy (130 mg, 60%). ^1H NMR (499 MHz, $CDCl_3$) δ 8.58 (d, J = 8.0, 1H), 8.22 (d, J = 7.9, 1H), 8.03 (d, J = 3.6, 1H), 7.97 (d, J = 7.7, 1H), 7.75 (m, 2H), 7.58 (t, J = 7.6, 1H), 7.44 (t, J = 7.7, 1H), 6.89 (d, J = 3.6, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.93, 134.65, 133.28, 131.64, 129.73, 128.65, 128.29, 127.22, 124.26, 123.59, 123.12, 122.83, 118.77, 116.80, 111.27.



Synthesis of Hippadine. Inside a glove box, triethylamine (37 mg, 0.36 mmol, 1.5 equiv), indole (28 mg, 0.24 mmol, 1 equiv), dimethylchlorosilane (34 mg, 0.36 mmol, 1.5 equiv) and THF (0.5 mL) were added to a dry vial. The mixture was stirred at room temperature for 6 h, at which time GC analysis showed full conversion of the indole. The reaction mixture was filtered through Celite, and the volatile materials were removed under vacuum. $[Ir(cod)Cl]_2$ (0.4 mg, 0.0006 mmol, 0.003 equiv), dtbpy (0.3 mg, 0.001 mmol, 0.005 equiv), B_2pin_2 (61 mg, 0.24 mmol, 1.0 equiv), HBpin (0.001 mL, 0.01 mmol, 0.05 equiv), and THF (0.4 mL) were added to the vial. The reaction mixture was heated at 80 °C for 6 h, at which time GC analysis indicated full conversion of the *N*-dimethylsilylindole. The reaction mixture was cooled to room temperature. The volatile materials were removed from the reaction mixture under high vacuum. $Pd(dba)_2$ (7.2 mg, 0.012 mmol, 0.05 equiv), PPh_3 (12.4 mg, 0.048 mmol, 0.20 equiv), methyl 6-bromo-1,3-benzodioxole-5-carboxylate (68 mg, 0.26 mmol, 1.10 equiv), K_3PO_4 (153 mg, 0.717 mmol, 3.00 equiv) and DMF (1 mL) were added to the reaction mixture. The reaction mixture was heated at 80 °C for 24 h. The reaction was filtered through Celite, washed with EtOAc, and concentrated under vacuum. Column chromatography (80:20 hexanes:ethyl acetate) afforded the known product judged to be pure by NMR spectroscopy (30 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 3.5, 1H), 7.94 (s, 1H), 7.87 (d, J = 7.6, 1H), 7.73 (d, J = 7.6, 1H), 7.60 (s, 1H), 7.45 (t, J = 7.7, 1H), 6.88 (d, J = 3.5, 1H), 6.15 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.35, 152.73, 148.72, 131.69, 131.10, 128.69, 124.15, 123.69, 122.84, 122.64, 118.54, 116.76, 110.98, 108.15, 102.57, 101.86.

5.6 References

(1) a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069; b) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036; c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(2) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.

(3) a) Ito, C.; Itoigawa, M.; Aizawa, K.; Yoshida, K.; Ruangrungsi, N.; Furukawa, H. *J. Nat. Prod.* **2009**, *72*, 1202; b) Ito, C.; Itoigawa, M.; Sato, A.; Hasan, C. M.; Rashid, M. A.; Tokuda, H.; Mukainaka, T.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2004**, *67*, 1488; c) Ito, C.; Katsuno, S.; Itoigawa, M.; Ruangrungsi, N.; Mukainaka, T.; Okuda, M.; Kitagawa, Y.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **1999**, *63*, 125.

(4) a) Heemstra, J. R.; Walsh, C. T. *J. Am. Chem. Soc.* **2008**, *130*, 14024; b) Dong, C.; Flecks, S.; Unversucht, S.; Haupt, C.; van Pee, K.-H.; Naismith, J. H. *Science* **2005**, *309*, 2216.

(5) Wiesner, W.; van Pee, K.-H.; Lingens, F. *FEBS Lett.* **1986**, *209*, 321.

(6) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

(7) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552.

(8) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899.

(9) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534.

(10) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.

(11) Wong, W.-Y.; Chow, W.-C.; Cheung, K.-Y.; Fung, M.-K.; Djurisic, A. B.; Chan, W.-K. *J. Organomet. Chem.* **2009**, *694*, 2717.

(12) Ortar, G. *Tetrahedron Lett.* **2003**, *44*, 4311.

(13) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(14) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.

(15) Mentzel, U. V.; Tanner, D.; Tonder, J. E. *J. Org. Chem.* **2006**, *71*, 5807.

Chapter 6. A Simple, Multidimensional Approach to High-Throughput Discovery of Catalytic Reactions

6.1 Introduction

Transition metal complexes catalyze many important reactions used in medicine, materials science and energy production. Most approaches to the design and discovery of new transition metal-catalyzed reactions begins with two or more substrates each containing a functional group (Figure 3). The substrates are generally chosen because it is hypothesized that they can undergo a reaction based on mechanistic insight, or because the product of their reaction would be of particular value. Another approach to the discovery of new chemical reactions and new transition metal catalysts is to expose two or more substrates each with a unique functional group to a transition metal catalyst, and to then perform an assay to identify reaction products. Although high-throughput methods for catalyst discovery that would mirror related approaches for the discovery of medicinally active compounds have been the focus of much attention, these methods have not been sufficiently general or accessible to typical synthetic laboratories to be adopted widely.

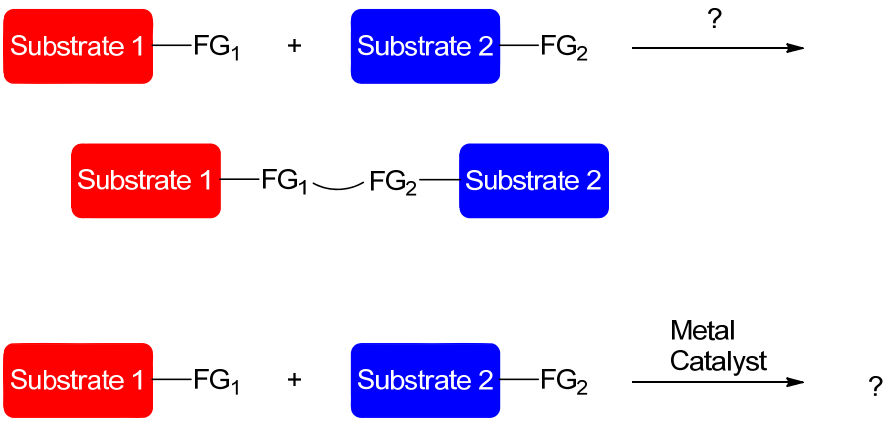


Figure 3. General approaches to the discovery of new chemical reactions and new catalysts

6.2 Background

Mechanistic data often provide the foundation for catalyst development and optimization. However, many reactions were discovered serendipitously while seeking a different synthetic transformation.[1] The advent of combinatorial methods for the discovery of new drug candidates and new enzymes for organic synthesis has raised the prospect of applying analogous high-throughput experimental methods to the discovery of catalytic transformations. Many studies on this topic have been published over the past two decades.[2] Although the experimental designs that have been reported all have merit, few, have been used by laboratories beyond those disclosing the original studies. Many of these approaches require cationic intermediates[2i,2j,2m,2n] acidic products,[3] substrates with colorimetric tags, serial optimization of portions of modular ligands,[4] the attachment of reactants to DNA fragments and PCR amplification to identify the product, or robotic equipment having a cost that is prohibitory to most laboratories. Thus, to apply combinatorial methods to catalyst discovery in a general fashion, new methods are

needed that require equipment commonly available in a synthetic laboratory or obtainable at a comparable cost.

Most published methods for the high-throughput discovery of catalysts evaluate one of the two catalyst-reactant dimensions. In other words, these methods have examined either many catalysts for a single class of reaction or a single catalyst for many reactions. A two-dimensional approach in which many catalysts for many catalytic reactions are tested simultaneously would create a more efficient discovery platform, if the reactants and products from such a system could be identified. Here, we disclose a method to discover catalytic reactions by conducting experiments in an x-y array on pools of substrates having similar masses, and analyzing combinations of these pools by mass spectroscopy. This format evaluates thousands of reactions at one time and pinpoints with just a few mass spectral measurements the coordinates of the metal and ligand that effect a reaction between two or more substrates. Using this method, we discovered a copper-catalyzed alkyne hydroamination and two nickel-catalyzed hydroarylation reactions, each of which displays excellent functional group tolerance.

6.3 Results and Discussion

For the study described here, the core experiment was conducted with a set of 17 organic reactants, each of which contains 10 to 13 heavy atoms (C, N, O, F, S) and possesses a single functional group (Figure 4). To facilitate implementation of this reaction discovery approach without the need to time-intensive synthesis of starting materials, we selected substrates which, with the exception of 1-butylindole, are commercially available. A reaction between two of these substrates would produce a product with a mass that would lie outside of the range of masses of the reactants. We

obtained mass spectral data by a combination of gas chromatography/mass spectrometry (GC/MS) to measure the masses of non-polar products and electrospray ionization mass spectrometry (ESI-MS) to measure the masses of polar products. Previously, custom mass spectrometers have been used to analyze by tandem MS-MS methods the activity of charged catalysts for reactions conducted in the gas phase. These examples have focused on comparing several catalysts for a single reaction, and require mass spectrometry instrumentation which is not available to most synthetic laboratories.[2m] The mass of potential products from joining two substrates is easily calculated from the masses of the reactants, including the masses of potential products formed with concomitant loss of common small molecules, such as H_2O, NH_3, H_2, and HCN, or common leaving groups, such as halides. Several additional design elements were used`, including the placement of different substituents on aryl groups to discriminate between them by their distinct mass spectral fragmentation patterns.

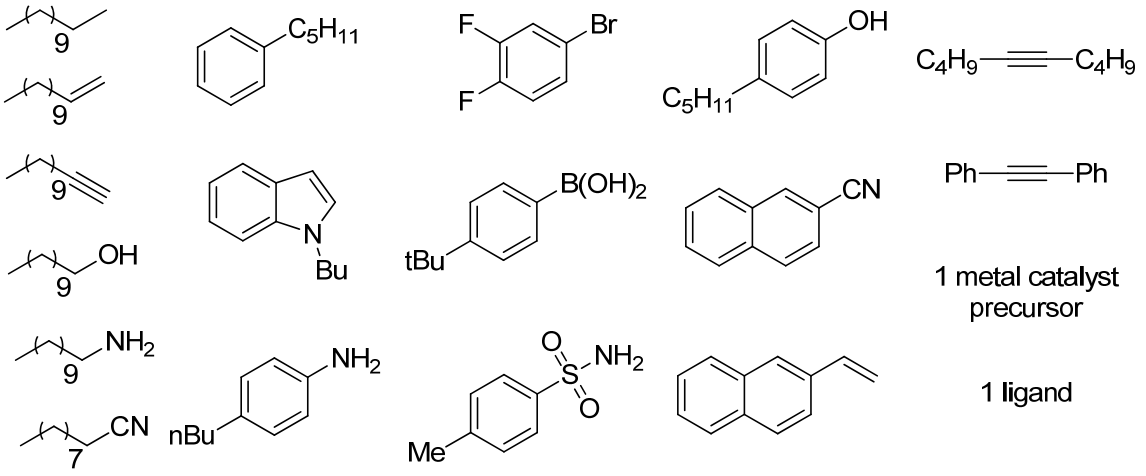


Figure 4. The combination of 17 substrates was placed into each reaction well.

A standardized method was devised to enable the simultaneous screening of substrates, metal catalyst precursors and ligands. Twelve ligands were dispensed, one into

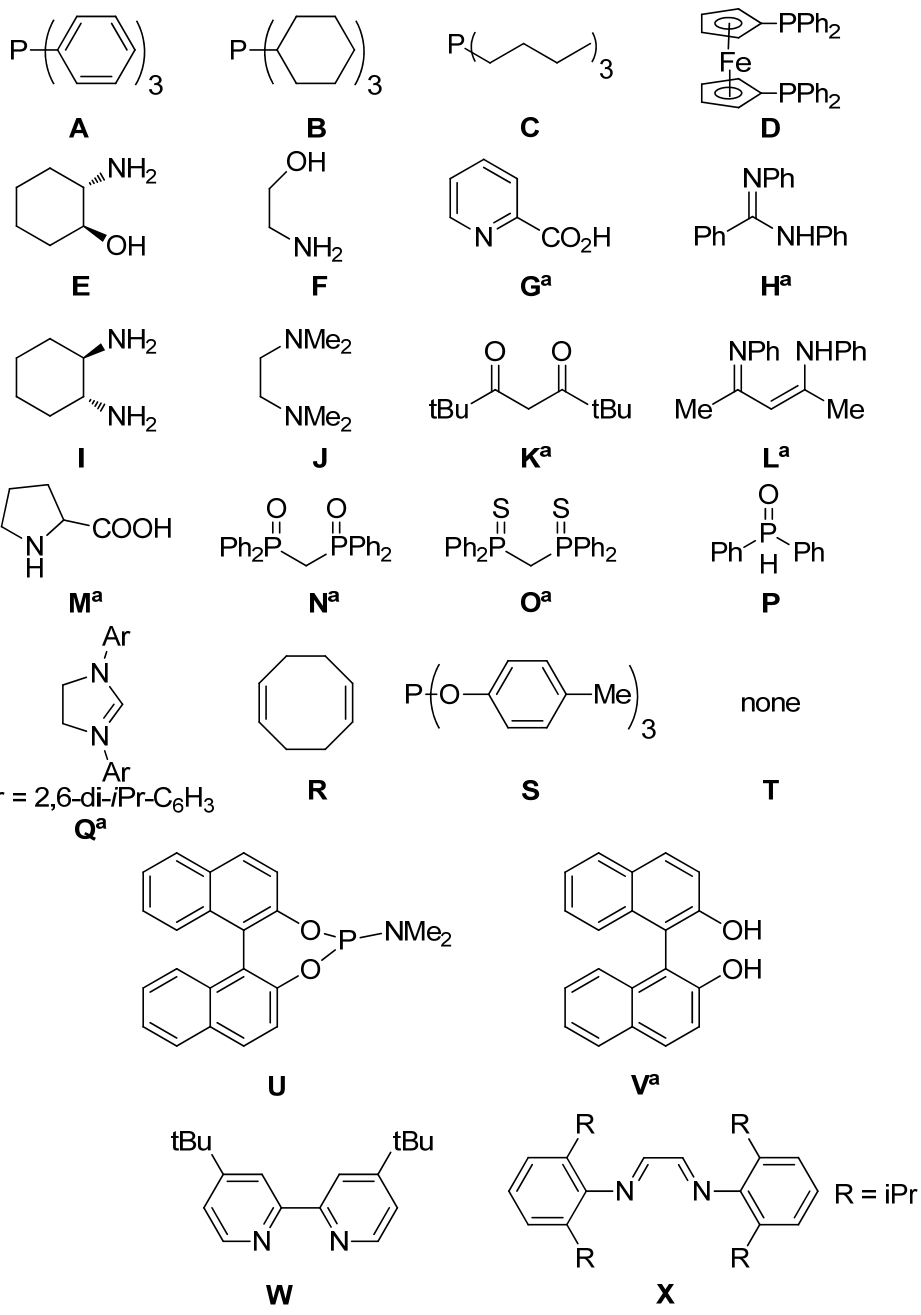
each well of a column, and eight metal catalyst precursors were dispensed, one into each well of a row. The plate was sealed and heated at 100 °C for 18 h. After this time, the contents of the wells in the plate were analyzed by mass spectrometry. The number of substrates is arbitrary; the 17 substrates contain a representative set, not a comprehensive set, of typical organic functional groups. A group of catalysts derived from Mn, Fe, Cr, Co, Cu, Ni, and W was chosen due to their abundance and low cost. In addition, we examined catalysts derived from Ru, Mo becuause these metals are inexpensive, Yb as a representative f-block metal, and Au because of its wide range of reactivity uncovered recently. The ligands we combined with these metals included common phosphines and amines, as well as less explored phosphine oxides, phosphine sulfides and amidinates (Table 18). Excess of the metal complexes were used in this system to alleviate poisoning all of the potential catalysts by one substrate. Reactions discovered in such a system would be rendered catalytic after initial identification of the transformation and metal-ligand combination that induces the transformation. The 17 substrates, in combination with catalysts derived from 15 metal centers and 23 ligands or the absence of a ligand, corresponds to more than 50,000 reactions. These reactions were conducted in a few days, after developing our protocol.

Table 18. Metal catalyst precursors and ligands used for the high-throughput reaction discovery protocol.

Metals

1) $Fe(acac)_2$
2) $FeCl_3$
3) $Mo(CO)_3(EtCN)_3$
4) $MoCl_5$
5) $Mn(acac)_2$
6) $W(CO)_3(MeCN)_3$
7) $Yb(OAc)_3$
8) $Cr(CO)_3(C_6H_6)$
9) $Co(OAc)_2$
10) $Ni(cod)_2$
11) CuCl
12) $Cu(OAc)_2$
13) $[Ru(p\text{-cymene})Cl_2]_2$
14) AuCl
15) $NiCl_2$-dme
16) none

Ligands



[a] Ligand activated with base before reaction

The catalyst components for the initial implementation of this strategy were chosen to identify earth-abundant metals that catalyze reactions previously induced by precious metal complexes. Although progress has been made toward the goal of catalyzing reactions using first-row transition metals, the smaller body of mechanistic information on reactions catalyzed by such systems makes high-throughput discovery methods to evaluate particularly appealing. The exact metals and ligands used in these experiments are depicted in Table 18. The reactions identified in this format would necessarily have the high degree of functional-group tolerance most often needed to prepare natural products and medicinally important compounds because they were identified in a medium containing a wide range of additional functional groups.

To minimize the number of mass spectra, in anticipation of conducting such studies on a large format, we analyzed reaction products by creating eight samples containing a portion of the contents of each row and twelve samples containing a portion of the contents of each column of a 96-well plate. By this method, only 20 mass spectra on each 96-well plate are needed to identify the x-y coordinates of the metal-ligand combination that gives rise to a reaction product. These coordinates correspond to the pooled samples of the row and column containing the same reaction product. In some cases, the product (and therefore the reaction partners) would be difficult to determine from the mass spectrum alone. Therefore, we devised an additional protocol to identify the product within a particular well by running a small set of additional experiments (*vide infra*).

Our design was implemented by conducting experiments in which the 17 reagents were combined in each of 384 wells (of a 16 x 24 array), all but one well containing one

metal precursor (15 total + one negative control containing no metal) and one ligand (23 ligands + one negative control containing no ligand). In this experiment, we included the substrates, metal-catalyst precursors, and ligands for three known reactions as positive controls. These reactions were the Ni-catalyzed carbocyanation of an alkyne,[5] the Cu-catalyzed oxidative coupling of an aromatic amine and an aryl boronic acid,[6] and the Ru-catalyzed alkylation of a sulfonamide with an alcohol (Figure 5-7).[7] The product from each of these three reactions was observed among the more than 50,000 possible catalytic reactions [(17•16/2 cross combinations of substrates + 17 homo-coupling of substrates) x 15 metal catalyst precursors x 24 ligands]. The GC-MS trace from the row containing $Ni(cod)_2$ revealed the product from carbocyanation of 5-decyne with 2-cyanonaphthalene, which eluted at 18.1 minutes and showed a molecular ion with an m/z value of 291 (Figure 5). The GC-MS trace from the row containing $Cu(OAc)_2$ revealed the diarylamine obtained from oxidative coupling of 4-*tert*-butylphenylboronic acid with 4-butylaniline, which eluted at 17.9 minutes and showed a molecular ion with an m/z value of 281 (Figure 6). Finally, the ESI-MS for the row containing $[Ru(p\text{-cymene})Cl_2]_2$ contained peaks corresponding to the mono-and dialkylation of *p*-toluenesulfonamide with 1-dodecanol (Figure 7) with m/z = 339 and m/z = 507. These positive control experiments showed that discrete transition metal-catalyzed reactions could be identified from a pool of substrates that could undergo thousands of possible binary reactions.

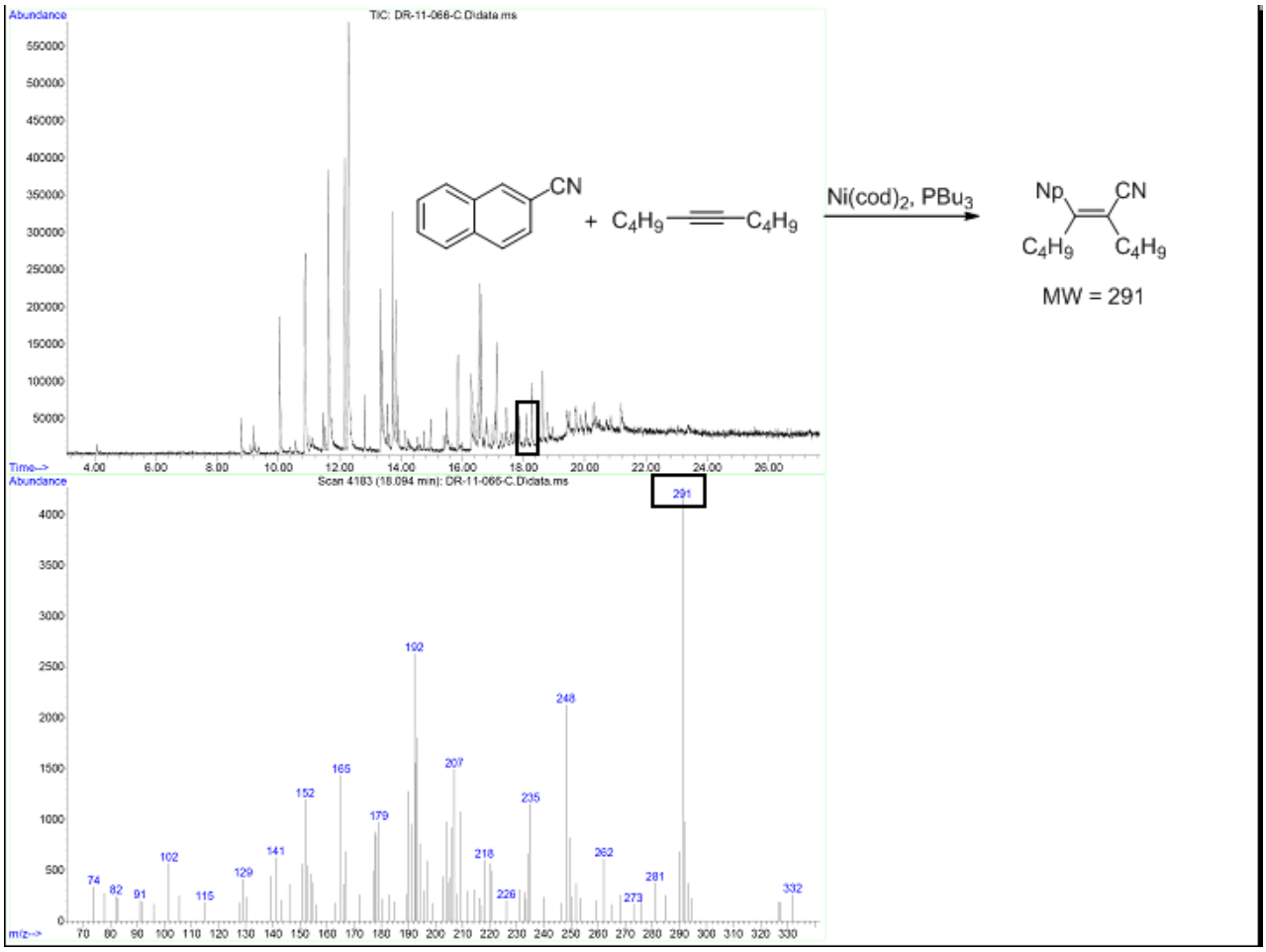


Figure 5. GC-MS of the combination of reactions in the row containing $Ni(cod)_2$ as a metal catalyst precursor. The product from Ni-catalyzed alkyne carbocyanation was also detected in the GC/MS for the column with PBu_3, indicating that the combination of $Ni(cod)_2$ and PBu_3 catalyzes the reaction. The peak at 18.1 minutes corresponds to material with an m/z = 291, which is the mass of the alkyne carbocyanation product.

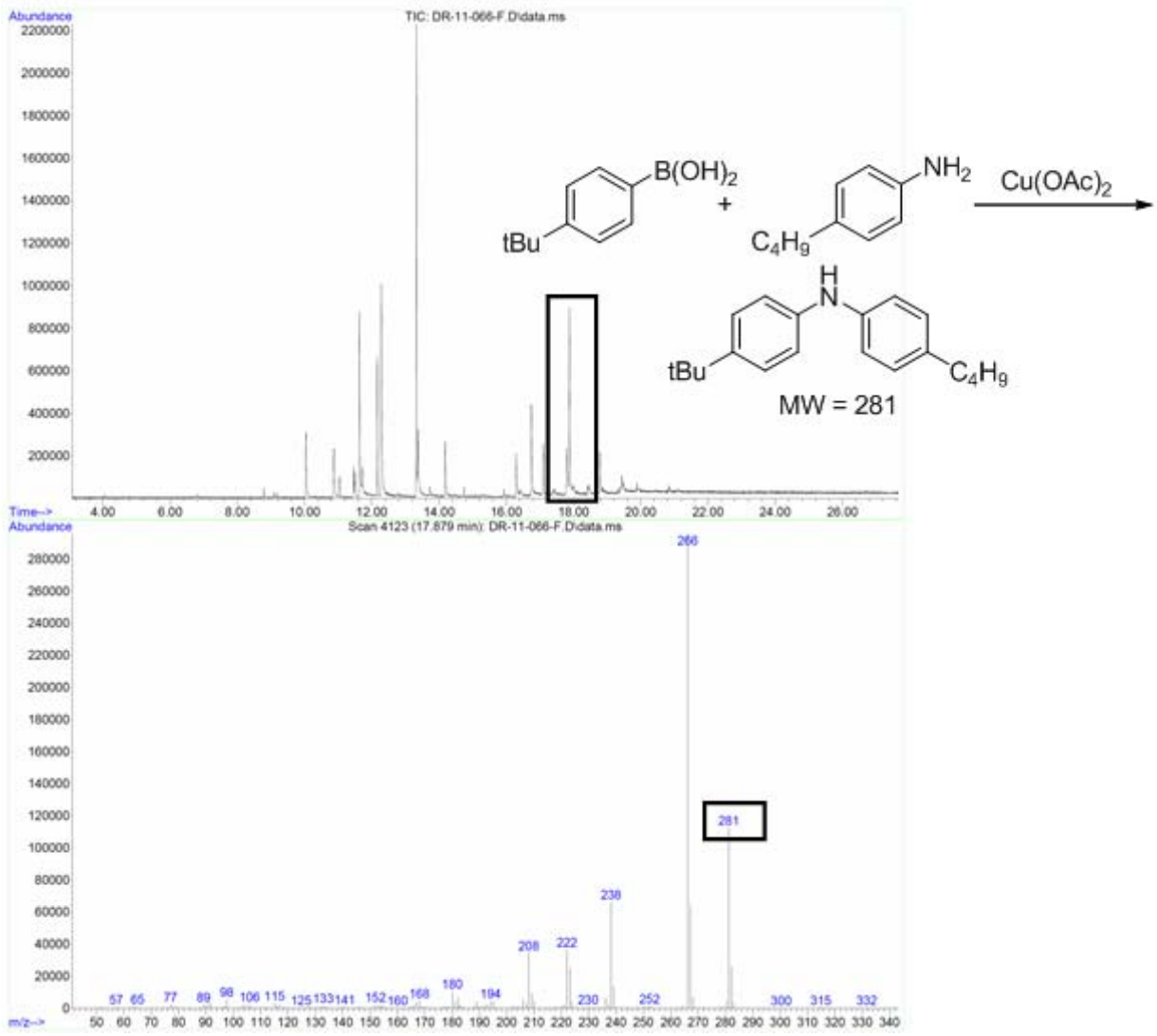


Figure 6. GC-MS of the combination of reactions in the row containing $Cu(OAc)_2$ as a metal catalyst precursor. The product from Cu-catalyzed oxidative coupling was observed. The peak at 17.9 minutes corresponds to material with an m/z = 281, which is the mass of the amination product.

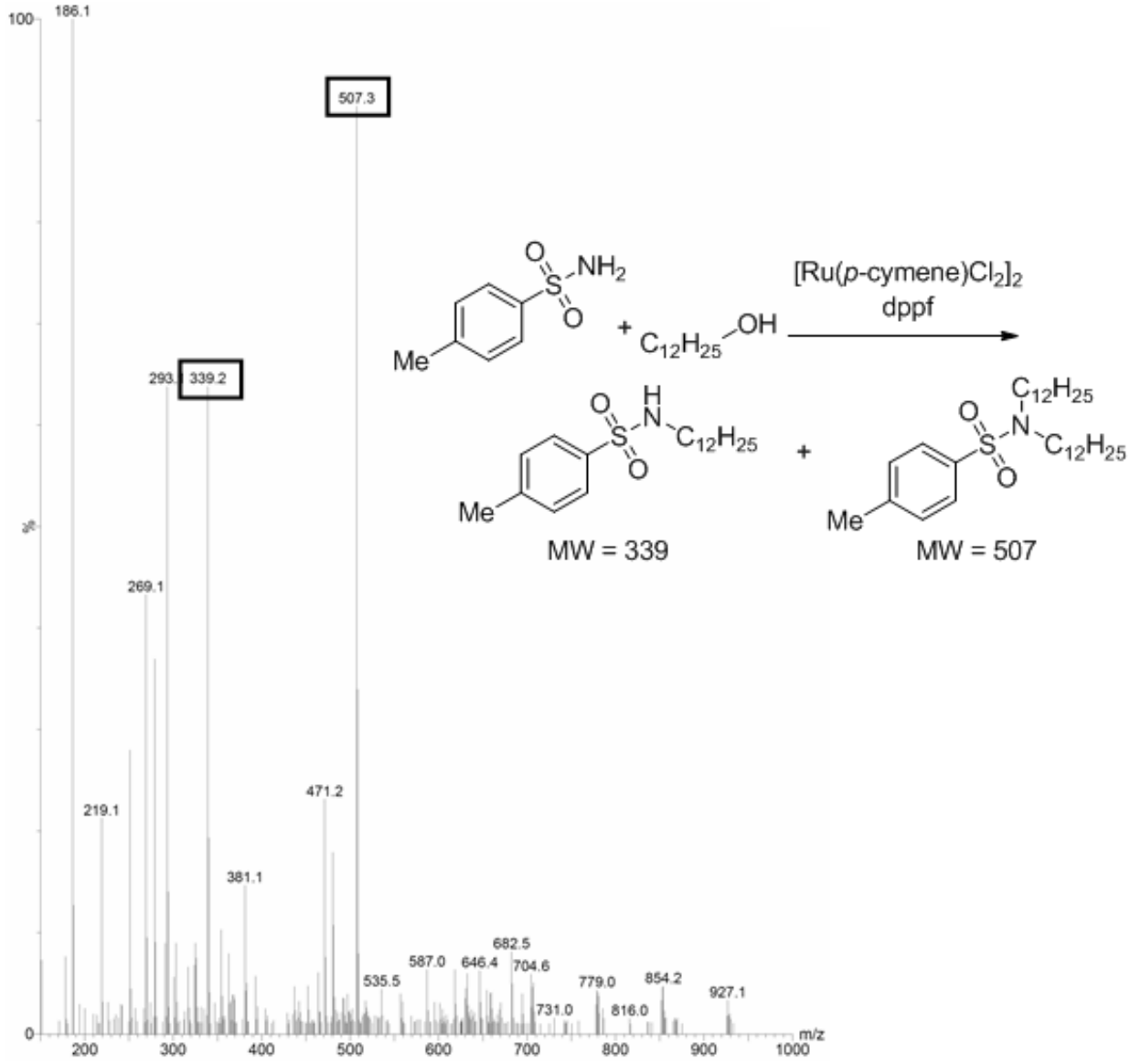


Figure 7. ESI-MS of the combination of reactions in the row containing [Ru(*p*-cymene)Cl_2]$_2$ as a metal catalyst precursor. The peaks at m/z = 339 and m/z = 507 correspond to the products from Ru-catalyzed sulfonamide monoalkylation and dialkylation, respectively.

In addition to the products of these positive control reactions, we observed the products from a reaction catalyzed by a first-row metal complex without ligand and a reaction catalyzed by a first-row metal complex containing a phosphine ligand. The GC-

MS of the solutions in the two rows containing CuCl and $Cu(OAc)_2$ consisted of a peak with a molecular ion having m/z = 315 (Figure 8). This product corresponds to that from coupling of 1-dodecyne with 4-butylaniline. This peak also appeared in the GC-mass spectra of the contents of the rows corresponding to reactions containing PBu_3 (C), the β-diketiminate ligand (L), and tri-*p*-tolylphosphite (S), as well as the row corresponding to reactions containing no ligand (T), indicating that the reaction occurs with the copper precursors alone and with the combination of the precursors and two of the phosphine ligands or the β-diketiminate ligand.

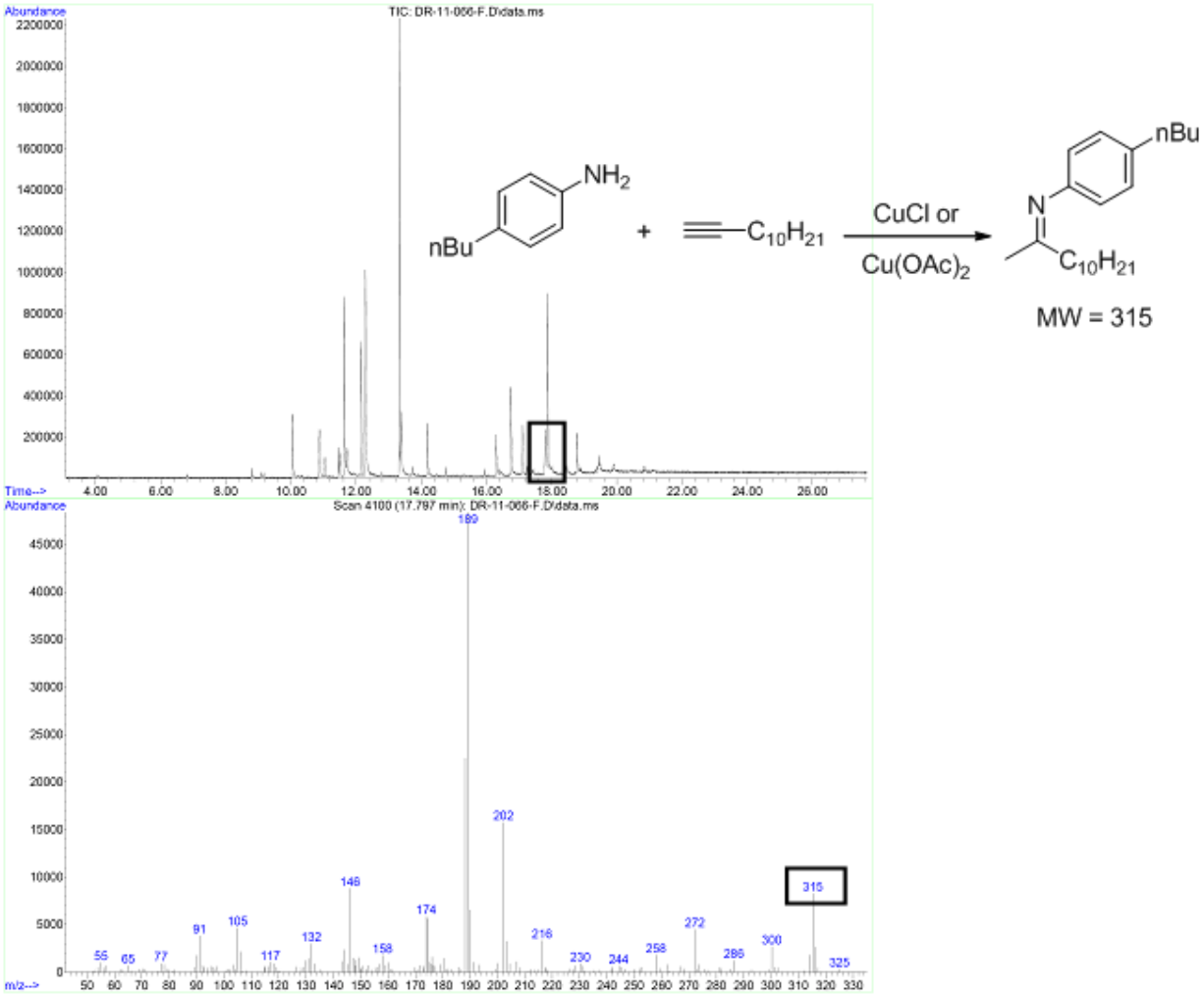
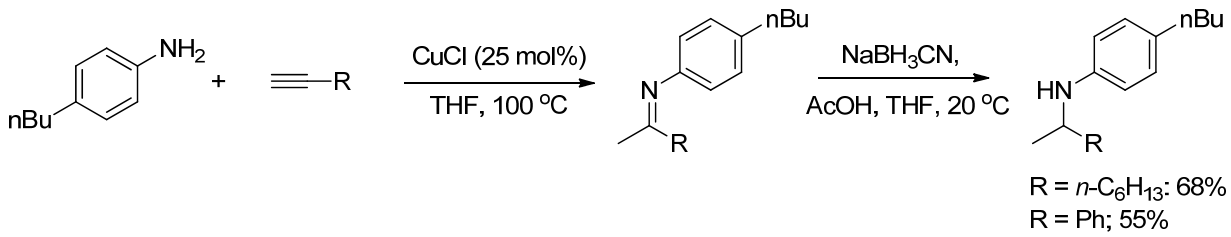


Figure 8. GC-MS of the combination of reactions in the row containing $Cu(OAc)_2$ as a metal catalyst precursor. The product of Cu-catalyzed alkyne hydroamination with an aromatic amine is observed. This product was also observed in the GC-MS of the combination of reactions in the columns containing $P(nBu)_3$, the nacnac-type ligand, tri-*p*-tolylphosphite and the column with no ligand. The peak at 17.8 minutes corresponds to material with an m/z = 315, which is the mass of the imine product. The same peak is observed for the row with CuCl as the metal catalyst precursor.

Separate experiments with the amine, alkyne, and catalyst components alone demonstrated that the reaction of the aromatic amine with the alkyne catalyzed by CuCl

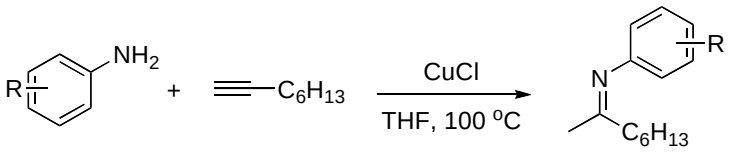
and $Cu(OAc)_2$ leads to the Markovnikov addition of the amine to the alkyne, followed by tautomerization to the corresponding imine (Scheme 52).[8] The products of these reaction could be isolated as the secondary amine following reduction with $NaBH_3CN$. Reactions catalyzed by CuCl occurred in higher yield than those catalyzed by $Cu(OAc)_2$. Reactions catalyzed by $Cu(OAc)_2$ yielded substantial product from Glaser coupling of the alkynes to form a diyne. Although this reaction occurs in the presence of three of the ligands identified in the combinatorial format, the reaction also proceeded rapidly in the absence of ligand. This copper-catalyzed reaction represents a rare hydroamination of an alkyne catalyzed by a first-row metal. [9] Intermolecular hydroamination of an alkyne has been reported with complexes of Group IV metals that are air sensitive and generally suffer from poor functional group compatibility, and it has been catalyzed by complexes of the precious metals palladium, rhodium and gold.[8c] Classical additions of amines to alkynes are conducted with toxic mercury compounds.



Scheme 52. Cu-catalyzed alkyne hydroamination with 4-*n*Bu-aniline

As shown by data in Table 19, this process occurs under conditions with 25 mol % of the inexpensive CuCl in good yield and tolerates an array of potentially reactive functional groups, such as nitriles, esters, ketones with enolizable hydrogens and unprotected alcohols, vindicating a core hypothesis of our experimental design.

Table 19. Selected copper-catalyzed alkyne hydroaminations with aromatic amines



Entry	R	Catalyst Loading	Yield*
1	4-nBu	10 mol%	57%
2	4-OH	25 mol%	80%
3	4-CN	25 mol%	51%
4	4-CO_2Me	25 mol%	68%
5	3-Br	25 mol%	84%
6	4-acetyl	25 mol%	60%
7	2,6-di-isopropyl	25 mol%	70%

* Yield determined by using gas chromatography with 1,3,5-trimethoxybenzene as an internal standard after hydrolysis with 1 M HCl at room temperature to 2-octanone

The GC-MS analysis from our experiment also revealed a reaction product eluting at 18.6 minutes with an apparent molecular ion having an m/z = 312. This peak was observed in the traces of the wells containing the combination of $Ni(cod)_2$ or $NiCl_2$-dme (Figure 9). This product was also observed in the GC-MS of the combination of reactions in the columns containing PPh_3, $P(nBu)_3$, PCy_3, dppf, dtbpy, Monophos, and SiPr, indicating that the reaction is catalyzed by the combination of a Ni precatalyst and these ligands. The peak at 18.6 minutes corresponds to material with an m/z = 312, which is the mass of the product from alkyne hydroarylation. Because the identity of this product

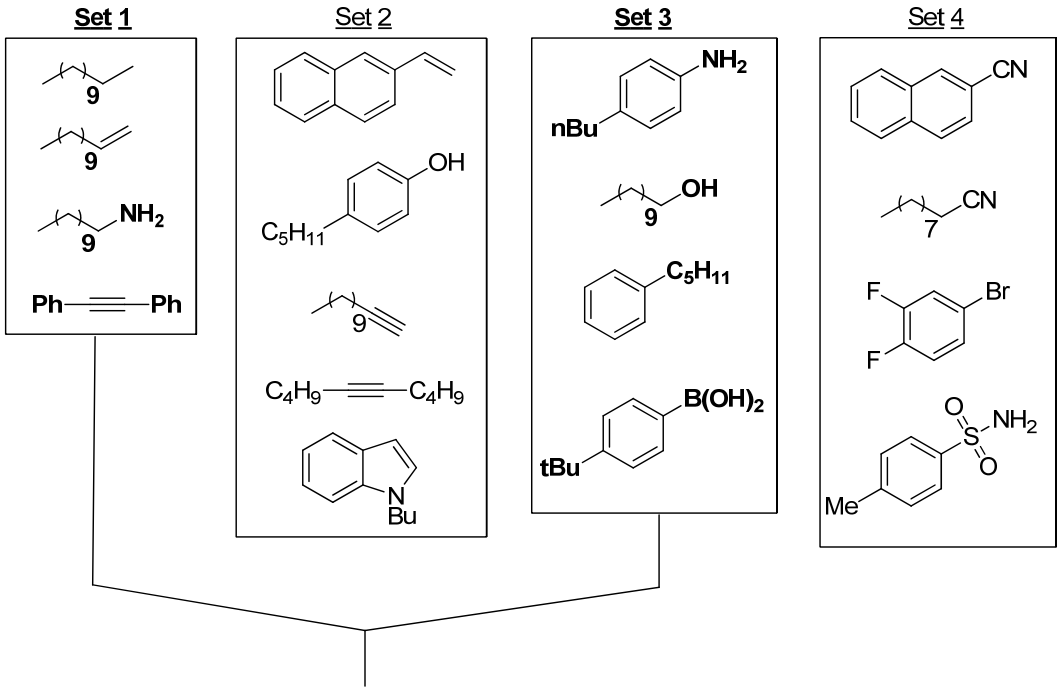
was not obvious from the mass spectrum, we devised a deconvolution strategy to determine the reactants that formed it.

Figure 9. GC-MS of the combination of reactions in the row containing $Ni(cod)_2$ as a metal catalyst precursor. The product of Ni-catalyzed alkyne hydroarylation with an aryl boronic acid was observed.

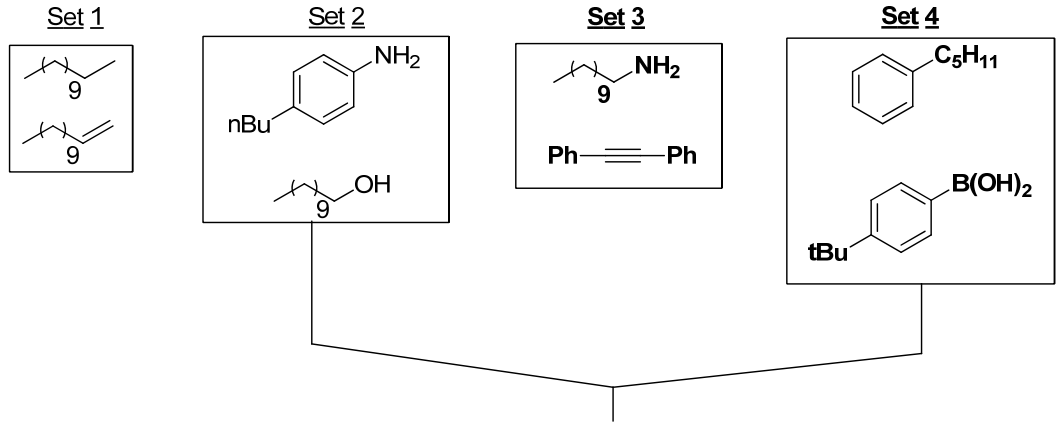
For this strategy, the potential reactants (in this case 17) were first divided into a small number of subsets, in this case three sets of 4 potential reactants and one set of five potential reactants (Figure 10; see Experimental Information for more details). The reactants in each of these sets were combined to create four pools of reactants. The pool

of reactants in one set was then allowed to react with the three other pools in the presence of the metal catalyst precursor and ligand that had been shown to form the unidentified product. These binary combinations of the four sets of substrates corresponded to just six reactions. In addition, to assess whether the coupling of two of the reactants requires a third component that could act as a ligand or promoter, three of the substrate sets were also allowed, in parallel, to react in a similar manner, for a total of ten reactions. This set of ten reactions identified the two sets that contained the reactants that formed the unknown product. The components of these two sets were then divided into four sets, each containing two substrates. In a similar manner, ten reactions were conducted in parallel with the metal catalyst precursor and ligand, and the two sets that yielded the desired product were identified. The four individual components of these sets were then allowed to react with each other in binary and ternary combinations. From these reactions, the two reactants that formed the unknown product were identified.

1st Round Substrate Sets



2nd Round Sets



3rd Round Sets

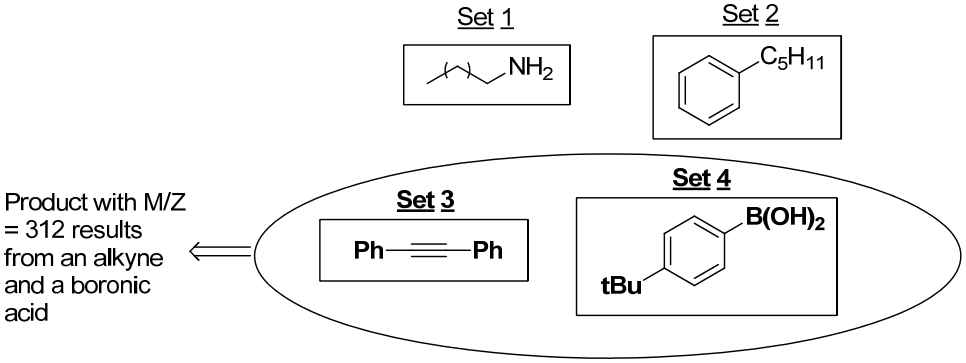


Figure 10. Deconvolution strategy to identify coupling partners for products observed in high-throughput reaction discovery

This short series of 3 x 10 reactions showed that the unknown product with m/z = 312 corresponded to the hydroarylation of diphenylacetylene with 4-*tert*-butylphenylboronic acid to yield a triarylalkene product. A similar strategy showed that an additional product in the wells containing $Ni(cod)_2$ and $P(nBu)_3$ that eluted at 16.6 min with a molecular ion of m/z = 292 (Figure 11) corresponded to a triarylalkene product from hydroarylation of diphenylacetylene with the haloarene 4-bromo-1,2-difluorobenzene. Examination of the combinations of $Ni(cod)_2$ and $NiCl_2$-dme with the ligands identified from the initial catalyst screening showed that $Ni(cod)_2$ and PPh_3 catalyzed the hydroarylation of diphenylacetylene with phenylboronic acid to yield triphenylethylene in good yield (Scheme 53). The reaction catalyzed by $Ni(cod)_2$ without added ligand formed just 15% yield of triphenylethylene. When the hydroarylation of diphenylacetylene was conducted with bromobenzene and the combination of $Ni(cod)_2$ and $P(nBu)_3$ as the catalyst, triphenylethylene was formed in less than 10% yield, but the same reaction with triethylsilane as a third component to act as a reducing agent furnished triphenylethylene in 71% yield (Scheme 53).This transformation of arylboronic acids has been reported most commonly with rhodium[10] and palladium[11] catalysts,[12] which contain costly precious metals.

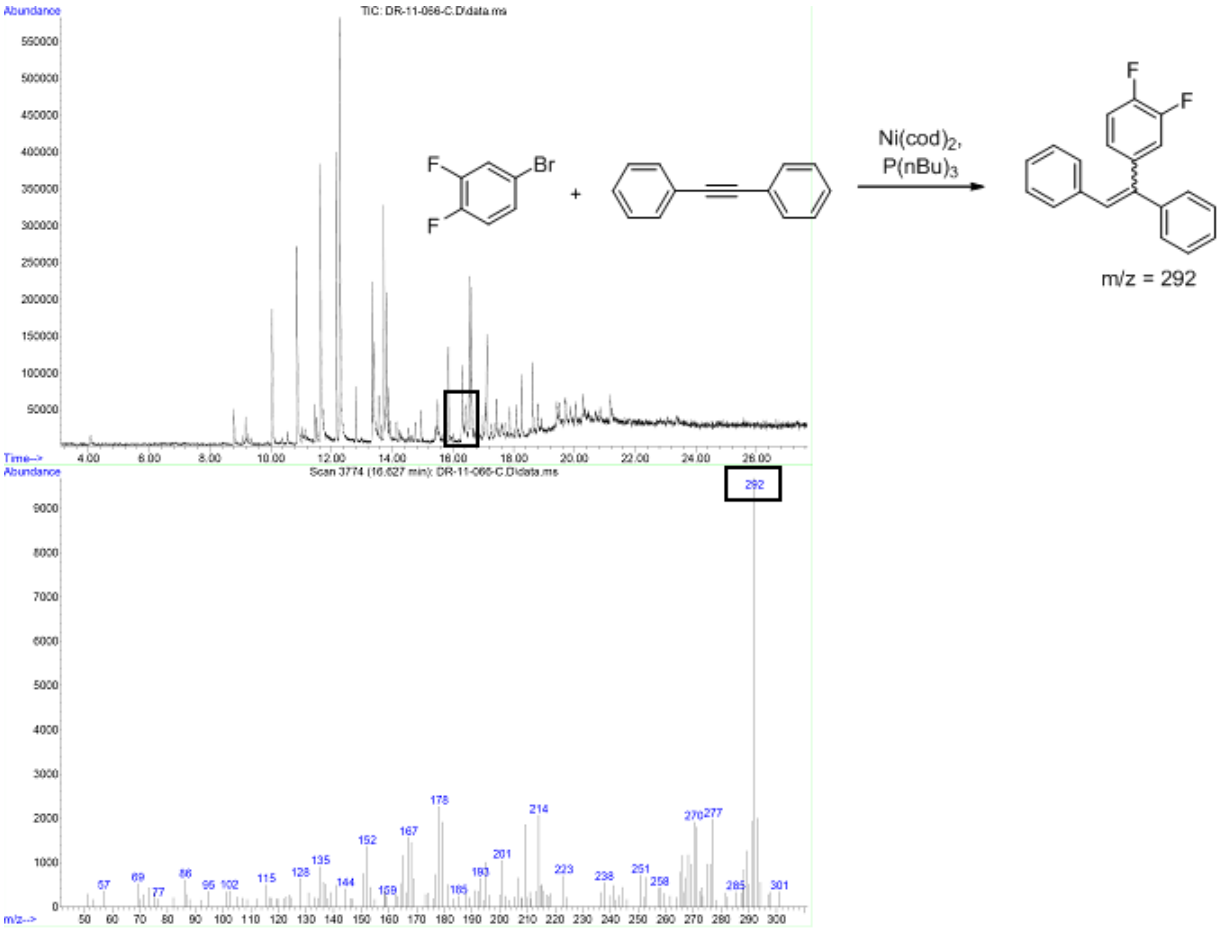
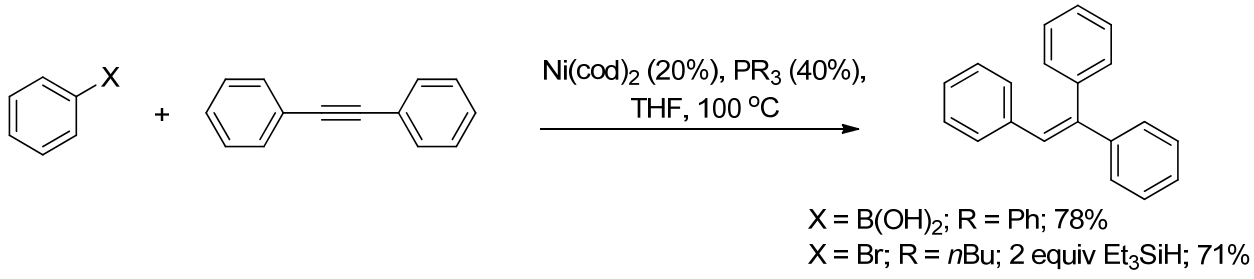


Figure 11. GC-MS of the combination of reactions in the row containing $Ni(cod)_2$ as a metal catalyst precursor. The product of Ni-catalyzed alkyne hydroarylation with an aryl bromide was observed.



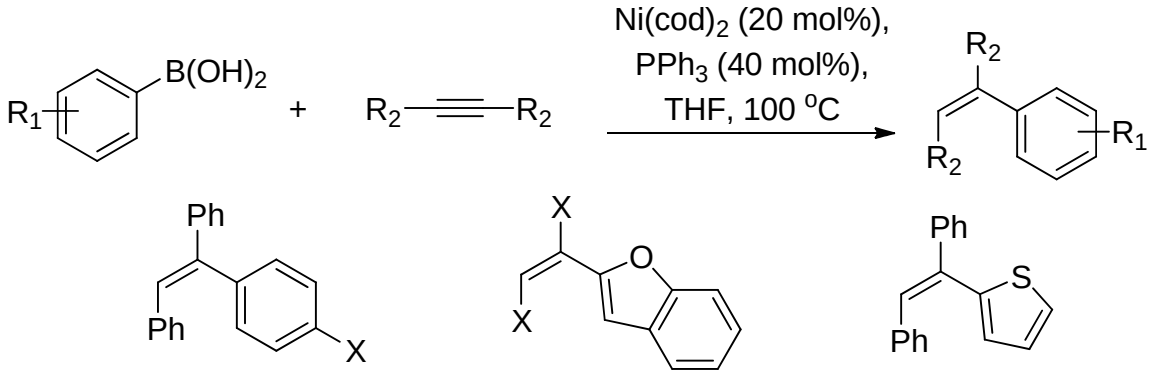
Scheme 53. Ni-catalyzed hydroarylation of diphenylacetylene with phenylboronic acid and bromobenzene

The synthesis of stereochemically defined trisubstituted alkenes is a challenging problem.[13] Such products are often prepared by stereo-controlled additions to alkynes, but fewer reactions give anti-addition products than give syn-addition products, and hydroarylations that give anti addition products are unknown. In contrast to this precedent, the major products of the two types of nickel-catalyzed hydroarylation discovered here result from anti addition to the alkyne in most cases. Likewise, the products from nickel catalyzed hydroarylation of an alkyne with the aryl halide and silane gave predominantly the anti-addition product. Moreover, the ligand affects the E/Z ratio from reaction of the arylboronic acid. The hydroarylation of diphenylacetylene with 4-*tert*-butylphenylboronic acid gave the addition product with an 8.7:1 ratio when the catalyst contained PPh_3, while reactions conducted with the catalyst generated from PCy_3 gave the addition product in a 1:3.8 ratio favoring the stereoisomer from syn addition. These stereochemical outcomes were unexpected and show the ability to use the discovery platform to identify reactions that occur with different selectivities, presumably, from mechanisms not followed by prior catalysts.

A survey of this nickel-catalyzed hydroarylation of alkynes with various boronic acids (Scheme 54) showed that this reaction, like the hydroamination we identified, tolerates a broad range of functional groups. The nickel-catalyzed hydroarylation of alkynes with aromatic boronic acids containing esters, nitriles, ketones with enolizable hydrogens, aryl chlorides, and aldehydes formed trisubstituted alkenes in good yield with generally good selectivity for the *Z* over *E* alkene geometry. High Z:E ratios were generally observed for arylboronic acids bearing electron-withdrawing groups, while aryl

boronic acids containing electron-donating substituents at the 4-position give ~1:1 mixtures of stereoisomers.

2-Heteroaryl boronic acids, which are unstable in many reactions,[14] also underwent this process to form the corresponding product from trans hydroheteroarylation of diphenylacetylene. Reaction of a heteroaryl boronic acid with an internal alkyne possessing alkyl substituents also formed the product of hydroheteroarylation.



X = CF_3; 91%; 8.3:1
X = CHO; 76%; 11.8:1
X = CN; 62%; >20:1
X = C(O)Me; 73%; 3.6:1
X = CO_2Me; 90%; 3.2:1
X = Cl; 83%; 11.3:1

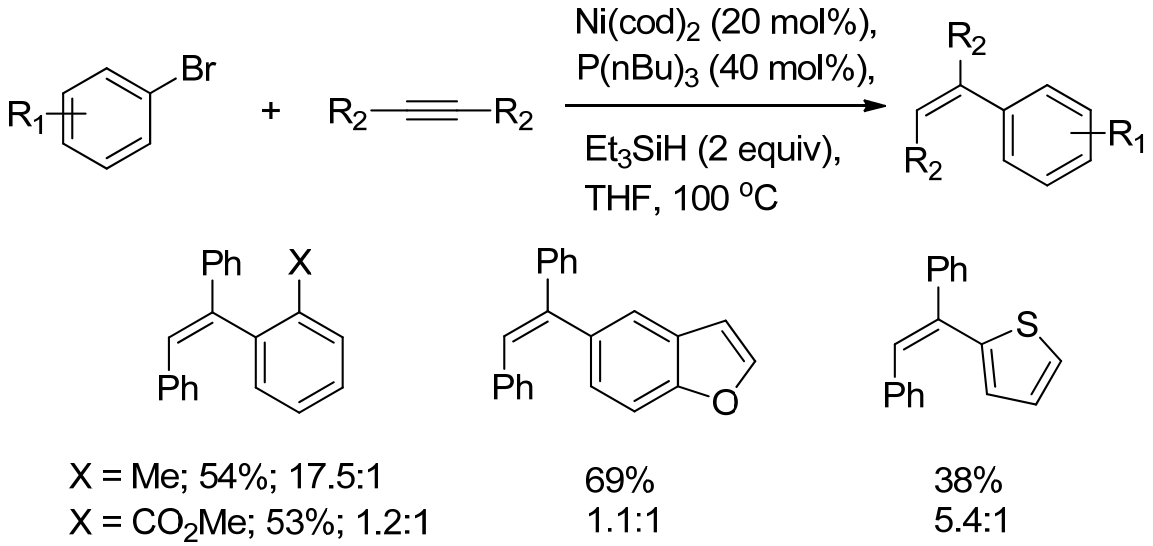
X = Ph; 95%; >20:1
X = C_2H_5; 55%;

89%
2.9:1

Scheme 54. Nickel-catalyzed alkyne hydroarylation with aryl and heteroaryl boronic acids. The ratio given is cis:trans (*Z*:*E*) olefin geometry.

Selected examples of the second type of alkyne hydroarylation we discovered involving aryl halides and triethylsilane are shown in Scheme 55. Although further studies are needed to identify the most effective combination of catalyst and reducing agent, our current studies show that the reactions of aryl halides containing potentially

reactive functional groups, as well as heteroaryl halides, form the trisubstituted alkenes with good to moderate selectivity for the product from formal trans addition. While the hydroarylation product could be observed in the reaction of diphenylacetylene with iodoarenes and chloroarenes, the yield for these reactions was lower than the reaction conducted with bromobenzene as the aryl halide. However, this result indicates that the scope of this reaction can be extended to other aryl halides.



Scheme 55. Nickel-catalyzed alkyne hydroarylation with aryl and heteroaryl bromides. The ratio given is cis:trans (*Z*:*E*) olefin geometry.

6.4 Conclusion and Outlook

This approach to reaction discovery holds significant potential to be used for purposes beyond those revealed in the current work. For example, this system could be used to explore reactions with additives, such as oxidants, reductants, acids, and bases and to explore reactions of two substrates with a third component, such as carbon monoxide or carbon dioxide. It could also be used to examine the reactivity of a single class of ligand with various organic substrates and transition-metal catalyst precursors.

Other current plans are to examine dual-metal catalyst systems for their ability to bring about new avenues to chemical reactivity, and to use this general approach to conduct more directed catalyst screening, such as focusing on reactive and highly valuable nitrogen heterocycles to examine their potential for reactivity with a wide range of organic substrates. While we have focused on the discovery of transition metal catalysts, because of the simplicity and generality of this approach, this system for multidimensional reaction discovery should be applicable to discovery of other catalyst types, such as heterogeneous catalysts, organocatalysts and biocatalysts. Thus, we anticipate that this approach to reaction discovery will provide a general and adaptable platform suitable for use by a wide range of laboratories for the discovery of a variety of catalytic reactions.

Following publication of our work, several other examples of similar approaches to the discovery of new reactions or new catalysts have been reported. MacMillan and co-workers have reported a method, which was termed "accelerated serendipity," in which a large number of random, binary combinations of substrates are mixed with various transition metal catalysts.[15] To facilitate this process, an automated workflow is utilized with the aid of robotic equipment. Each of the reactions is then assayed by GC-MS to identify new reactions. With this approach to high-throughput reaction discovery, MacMillan and co-workers found a C-H arylation reaction at the α–position of amines with electron-deficient aryl nitriles catalyzed by an iridium photoredox catalyst and visible light.

Taran and co-workers have utilized a sandwich immunoassay in which binary combinations of tagged substrates are mixed and exposed to a transition metal catalyst.[16]

The immunoassay is then used to pull out reactive combinations and to identify the substrates undergoing reaction. Application of this system allowed for the discovery of a copper-catalyzed coupling of thioureas and phenols to yield isoureas and a copper-mediated cyclization of alkynes and *N*-hydroxythioureas to form thiazole derivatives. While this system requires initial synthesis of a library of substrates, its high-throughput capability allows for efficient examination of catalysts.

A collaboration between Bellomo, Houk and the process chemistry division of Merck Research Laboratories has developed a method to use microscale parallel screening to discover a new method for the synthesis of pyrimidinones.[17] Pyrimidinones constitute the core structure of an important class of HIV integrase inhibitors. The goal of this investigation was to develop and apply a microscale screening platform to discover a catalyst for the synthesis of pyrimidinones from a linear, *N*-hydroxyamidine precursor. The platform that was developed enabled a single scientist to assemble and analyze 475 reactions in a single day. With this approach, the team discovered a new copper catalyst for the synthesis of pyrimidinones with low catalyst loading under mild conditions, whereas the previous methods for the synthesis of this structure required heating at very high temperatures. This approach demonstrates how high-throughput experimentation can be used to rapidly improve a single reaction without a need for detailed mechanistic insight. However, this approach to reaction discovery and improvement relies upon access to specialized equipment and the availability of large libraries of metal catalysts, ligands, and various additives.

As the recent development of several methods for high-throughput reaction discovery demonstrates, this approach to the discovery of new reactions and catalysts will

likely be a topic of future investigation. The development of better screening approaches and more rapid analysis techniques will prove crucial in the improvement of this approach to catalyst discovery. Many of the catalysts and reaction discovered using these approaches will address unmet synthetic challenges and eventually find use in targeted small molecule synthesis.

6.5 Experimental Information

Methods

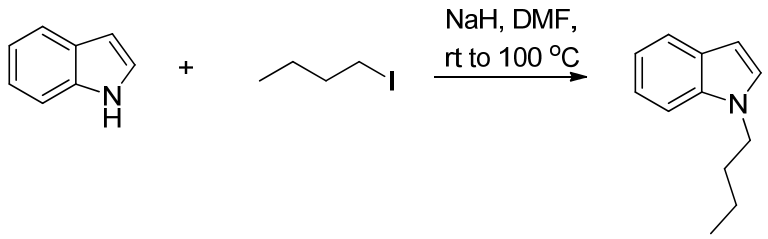
All reactions were conducted under an argon or nitrogen atmosphere in flame-dried glassware or in an Innovative Technologies drybox. Dry and degassed solvents were used unless otherwise noted. Column chromatography was performed with a Teledyne Isco Combiflash® R_f system with Redi*Sep* R_f columns.

Materials. $Fe(acac)_2$, $MoCl_5$, CuCl, $FeCl_3$, $NiCl_2$-dme $Mn(acac)_2$, (benzene)$Cr(CO)_3$, $Co(OAc)_2$, $Yb(OAc)_3$, $W(CO)_3(MeCN)_3$, PPh_3, $PnBu_3$, PCy_3, 2-aminocyclohexanol HCl, ethanolamine, 2-picolinic acid, 4,4'-di-*tert*-butylbipyridine, TMEDA, *trans*-1,2-diaminocyclohexane, BINOL, *cis,cis*-1,5-cyclooctadiene (cod), 2,2,6,6-tetramethylheptane-3,5-dione, diphenylphosphine oxide, L-proline, dodecane, 1-dodecene, 1-dodecanol, 1-dodecylamine, *p*-toluenesulfonamide, 4-bromo-1,2-difluorobenzene, 4-pentylphenol, 2-cyanonaphthalene, diphenylacetylene, triethylsilane, triethylamine, NaO*t*Bu, 1-octyne, $NaBH_3CN$, AcOH, DMF, indole and 1-iodobutane were purchased from Aldrich Chemicals and used as received. $Ni(cod)_2$, [Ru(*p*-cymene)$Cl_2]_2$, $Cu(OAc)_2$ (anhydrous), $Mo(CO)_3(EtCN)_3$, AuCl, 1,1'-Bis(diphenylphosphino)ferrocene, and Monophos were purchased from Strem Chemicals and used as received. 1-dodecyne, decanonitrile, *n*-pentylbenzene, 2-vinylnaphthalene, and 5-decyne were purchased from Alfa Aesar and used as received. 4-*n*-Bu-aniline was purchased from TCI America and used as received. Aryl and heteroaryl boronic acids were purchased from CombiBlocks and used as received. N-((Z)-4-(phenylamino)pent-3-en-2-ylidene)aniline,*(47)* Methylenebis(diphenylphosphine oxide)*(48)*, and Methylenebis(diphenylphosphine sulfide)*(49)* were prepared by literature methods. NaH

was purchased from Aldrich Chemicals as a 60% dispersion in mineral oil, washed with pentane and dried under vacuum before use. *Z*-1,2-diphenylethenyl tosylates was prepared according to a literature report.*(50)*

Instruments. GC-MS data were obtained on an Agilient 6890-N GC system containing an Alltech EC-1 capillary column and an Agilient 5973 mass selective detector. ESI-MS data were obtained with a Waters ZMD Quadropole Instrument with a photomultiplier detection system and a 1:1 MeCN:H_2O mobile phase.

Experimental Procedures and Information



Synthesis of *N*-Bu-indole. Inside a glovebox, indole (1.17 g, 10.0 mmol, 1.00 equiv), NaH (240 mg, 10.0 mmol, 1.00 equiv) and dry DMF (10 mL) were mixed in a dry vial at room temperature for 2 h. After 2 h, 1-iodobutane (2.03 g, 11.0 mmol, 1.10 equiv) was added, and the vial was heated at 100 °C for 2 h. After 2 h, the mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and the resulting solution was concentrated under vacuum. The residue was purified by flash column chromatography (0-5% EtOAc in hexanes) to give pure *N*-Bu-indole (951 mg, 55%). Spectral properties matched those of previous reports containing the preparation of this compound.

Assembly of 96-well plates for high-throughput discovery. An aluminum 96-well plate (see Picture 1 and Picture 2 below) was filled with ~ 1 mL glass tubes (Kimble Reusable Borosilicate Glass Tubes with Plain End O.D. x L: 6 x 50mm; available from Fisher Scientific), dried in an oven and brought into a nitrogen-filled glovebox. Stock solutions of each metal catalyst precursor were prepared with the following masses of each metal and 1.2 or 2.4 mL of THF.

Metal Catalyst Precursor	**Mass per Well (mg)**	**Total Mass (mg)**
1) $Fe(acac)_2$	3.8	45.8
2) $MoCl_5$	4.0	48

3) $Ni(cod)_2$	4.2	49.6
4) $[Ru(p\text{-cymene})Cl_2]_2$	4.6	55.2
5) CuCl	1.6	19.2
6) $Cu(OAc)_2$	2.8	32.8
7) $FeCl_3$	4.6	56.2
8) $NiCl_2$-dme	3.3	39.6
9) $Mn(acac)_2$	3.8	45.6
10) $Co(OAc)_2$	2.7	31.9
11) AuCl	3.5	41.9
12) $(benzene)Cr(CO)_3$	3.3	38.5
13) $W(CO)_3(MeCN)_3$	5.9	70.4
14) $Yb(OAc)_3$	5.3	63.1
15) $Mo(CO)_3(EtCN)_3$	5.2	62.2
16) None	-	-

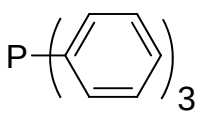
The metal catalyst precursors were then added to the tubes in the plate by adding 0.1 mL (1.2 mL stock solution) or 0.2 mL (2.4 mL stock solution) to each tube of the appropriate row. Metal catalyst precursors (3, 5-8, 10, 14) that were not soluble were added individually to the appropriate tubes.

Stock solutions of each ligand (see table below for structures) were prepared with 0.8 mL or 1.6 mL of THF and the masses of the ligands shown below.

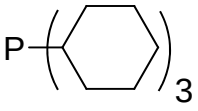
Ligand	**Mass per Well (mg)**	**Total Mass (mg)**
A) PPh_3	7.8	62.8
B) PCy_3	8.4	67.2
C) $PnBu_3$	6.1	48.8
D) dppf	8.4	67.2
E) 2-aminocyclohexanol HCl	2.2	18.2
F) Ethanolamine	1.0	8.0
G) 2-picolinic acid*	1.8	14.8
H) *N,N'*-diphenylbenzimidamide*	4.1	32.8
I) *Trans*-1,2-diaminocyclohexane	1.8	14.4
J) TMEDA	1.8	14.4
K) Tetramethylheptanedione*	2.8	22.4
L) *N*-((Z)-4-(phenylamino)pent-3-en-2-ylidene)aniline*	3.8	30.4
M) L-proline*	1.8	14.4
N) Methylenebis(diphenylphosphine oxide)*	6.3	50.4
O) Methylenebis(diphenylphosphine sulfide)*	6.8	54.4
P) Diphenylphosphine oxide	6.1	48.8
Q) SIpr-HCl*	6.4	51.2

R) Cod	3.2	25.6
S) $P(O\text{-}p\text{-}tol)_3$	10.6	84.8
T) None	-	-
U) Monophos [(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl) dimethylamine)	5.4	43.2
V) BINOL	4.2	34.4
W) 4,4'-di-*tert*-butylbipyridine	4.0	32
X) (N,N'E,N,N'E)-N,N'-(ethane-1,2-diylidene)bis(2,6-diisopropylaniline)	5.6	45.2

The ligands were then added to the tubes in the plate by adding 0.1 mL (0.8 mL stock solution) or 0.2 mL (1.6 mL stock solution) to each tube of the appropriate row. Ligands (D, E, G, M, N, O, Q) that were not soluble were added individually to the appropriate tubes (To the tubes containing ligand precursors that were activated with base (*), 2 mg of NaO*t*-Bu was added as a solution in dry THF.



A



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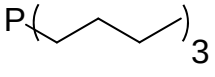

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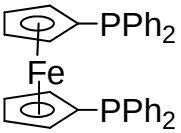

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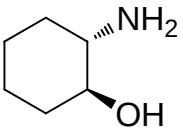

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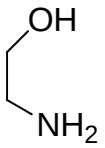

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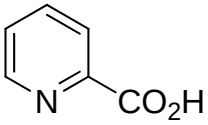
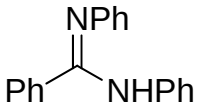
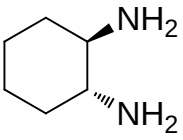


G[a]



H[a]



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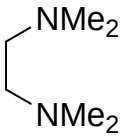

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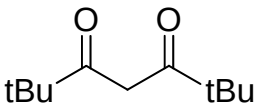

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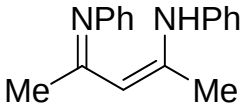

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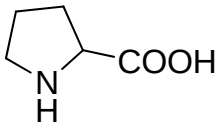

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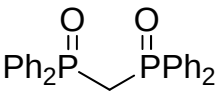
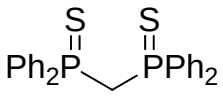
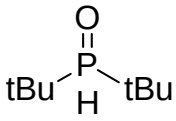


N[a]



O[a]



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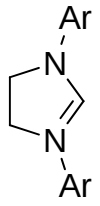
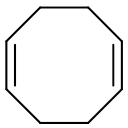
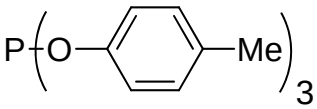


Q[a]



R



S

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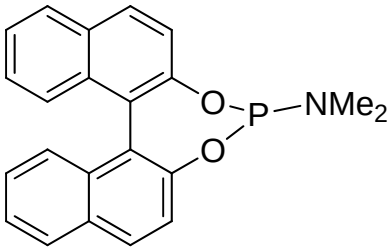
T



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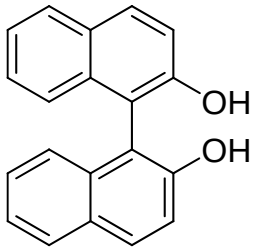

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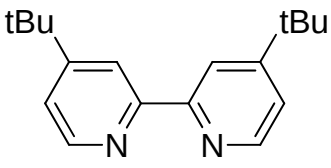
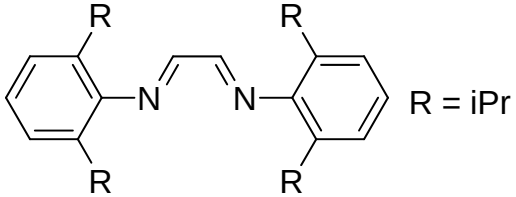


W



X

[a] Ligand activated with base before reaction

The plate with the tubes containing the metal catalyst precursors and ligands were then heated at 40-50 °C inside the glove box to evaporate the solvent.

To an oven-dried 25 mL volumetric flask was added the following masses of each substrate.

Substrate	**Total Mass (mg)**	**Mass per Well (mg) after dispensing the stock solution**
Dodecane	245	2.6
1-dodecene	242	2.5
1-dodecyne	240	2.5
1-dodecanol	268	2.8
1-dodecylamine	267	2.8
Decanonitrile	221	2.3
4-bromo-1,2-difluorobenzene	278	2.9
2-vinylnaphthalene	222	2.3
p-toluenesulfonamide	247	2.6
Diphenylacetylene	257	2.7
4-*n*-pentylphenol	237	2.5
2-cyanonaphthalene	221	2.3
4-*tert*-butylphenylboronic acid	257	2.7
5-decyne	200	2.1
n-pentylbenzene	214	2.2
4-*n*-Bu-aniline	215	2.2

N-Bu-indole	250	2.6

Following addition of the substrates to the volumetric flask, the mixture was diluted with dry THF to a volume of 25 mL. This solution was then transferred to a separate dry glass container, and the volumetric flask was washed with an additional 4 mL of THF for a total volume of 29 mL. A 0.3 mL aliquot of this solution was then added to each of the 96 tubes in the plate (29 mL/96 wells = 0.30 mL/well). The plate containing the glass tubes was then heated at 40-50 °C inside the glove box to evaporate the solvent.

After evaporation of the solvent, the well plate was sealed by placing a sheet of Teflon® over the glass tubes and placing a smooth metal plate on top of the well plate. The top plate was fixed into place with bolts tightened with a torque wrench. This sealed well plate was then heated on a standard heating plate for 18 h at 100 °C (See Picture 3 below). Following heating, the reaction assembly was removed from the heating plate and cooled to room temperature. After cooling, the assembly was removed from the glove box. A set of eight 4 mL vials was labeled A, B, C, D, E, F, G, and H for each of the 8 rows in the well plate. A set of 12 4 mL vials was labeled 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 for each of the columns in the well plate, making a total of 20 vials. 0.5 mL of CH_2Cl_2 was added to each of the 96 glass tubes, and 2 samples were removed from each glass tube: one sample was placed in the 4 mL vial corresponding to the row and one sample was placed in the 4 mL vial corresponding to the column. For example, a sample from tube A1 was placed in both vial A and vial 1. After this distribution of aliquots was completed for each of the 96 glass tubes, the contents of the 20 4 mL vials labeled A-H and 1-12 was filtered through a plug of Celite in a pipette into a GC vial, washing with ethyl

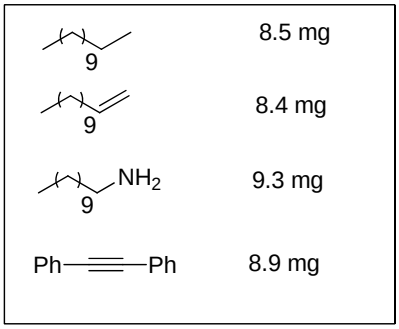
acetate. These vials were analyzed by GC-MS. A sample was removed from each of the samples for GC-MS analysis, placed into a separate GC vial, and diluted with MeOH. These samples were analyzed by ESI-MS.

Following analysis of each of these samples by GC-MS and ESI-MS, the mass spectral data were analyzed. In each of the GC-MS chromatograms, the organic substrates eluted between 0 and 13.5 minutes. The masses of peaks for material eluting between 13.5 minutes and the end of the GC-MS method were determined. In the ESI-mass spectra, significant peaks in the appropriate mass range for the reaction of two of the organic substrates were identified. After the mass(es) of product(s) had been determined, a spreadsheet (see spreadsheet below) containing potential product masses was used to identify the possible combinations of substrates that could form a product with the observed mass. To use this spreadsheet efficiently, a search for the product mass was conducted with Microsoft Excel. When two potential reactive substrates were identified, two independent reactions were conducted: one reaction with the two substrates (0.05 mmol each), the metal catalyst precursor (0.05 mmol) and THF (0.1 mL) and one reaction with the two substrates (0.05 mmol each), the metal catalyst precursor (0.05 mmol), the ligand (0.05 mmol) and THF (0.1 mL). These independent reactions were then assayed by GC-MS or ESI-MS to confirm the assignment of the reaction components leading to the observed product.

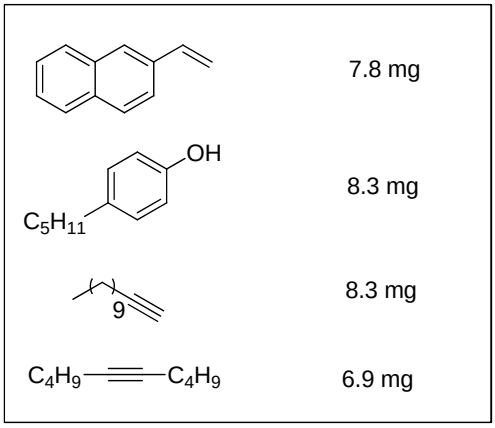
Reaction Deconvolution Scheme for identification of the product of the hydroarylation of diphenylacetylene with 4-*tert*-butylphenylboronic acid. To determine the two substrates that led to the observed reaction product when we were unable to identify the product from the mass spectrum, the following deconvolution scheme was followed. This scheme could be used generally to find the two reactants that lead to an observed product. First, the 17 substrates used in the high-throughput reaction discovery system were divided into 4 groups, as shown below.

1st Generation Groups

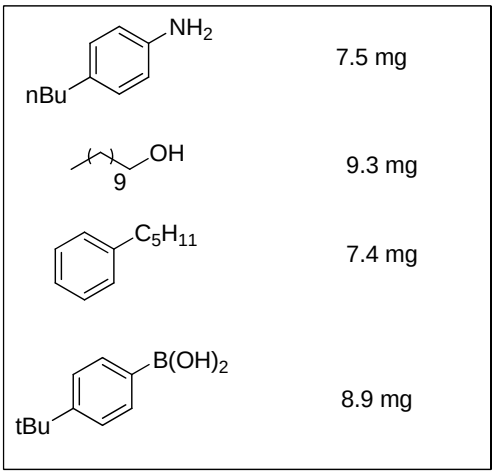
Group 1



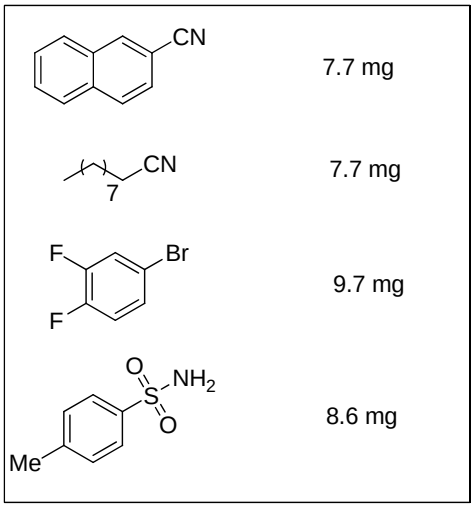
Group 2



Group 3



Group 4



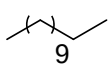
A set of 10 reactions was then assembled. $Ni(cod)_2$ (6.9 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), the substrates (the masses are shown in the table below) and THF (0.2 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 18 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC-MS. Each reaction was then evaluated to determine if it contained the product observed during the catalyst screening.

Reaction #	Substrate Groups	Product Detected by GC-MS?
1	1,2	No
2	1,3	Yes
3	1,4	No
4	2,3	No
5	2,4	No
6	3,4	No
7	1,2,3	Yes
8	1,2,4	No
9	1,3,4	Yes
10	2,3,4	No

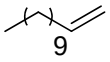
From these results, it was determined that the reaction occurred between a substrate from Group 1 and a substrate from Group 3. The substrates in Group 1 and Group 3 were then divided into 4 2nd generation groups shown below.

2nd Generation Groups

Group 1

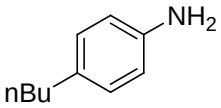


8.5 mg

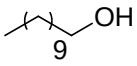


8.4 mg

Group 2

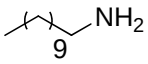


7.5 mg

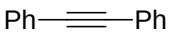


9.3 mg

Group 3

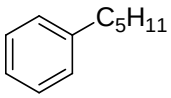


9.3 mg

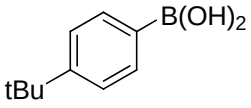


9 mg

Group 4



7.4 mg



8.9 mg

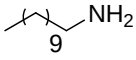
The same set of reactions with the same catalyst loading, temperature and time was then performed with these substrate groups. The results are shown in the following table.

Reaction #	Substrate Groups	Product Detected by GC-MS?
1	1,2	No
2	1,3	No
3	1,4	No
4	2,3	No
5	2,4	No
6	3,4	Yes
7	1,2,3	No
8	1,2,4	No
9	1,3,4	Yes
10	2,3,4	Yes

From these results, it was determined that the reaction occurred between a substrate from Group 3 and a substrate from Group 4. The substrates in Group 3 and Group 4 were then divided into four groups shown below.

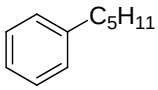
3rd Generation Groups

Group 1



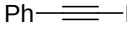
9.3 mg

Group 2



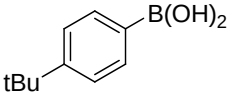
7.4 mg

Group 3



9 mg

Group 4

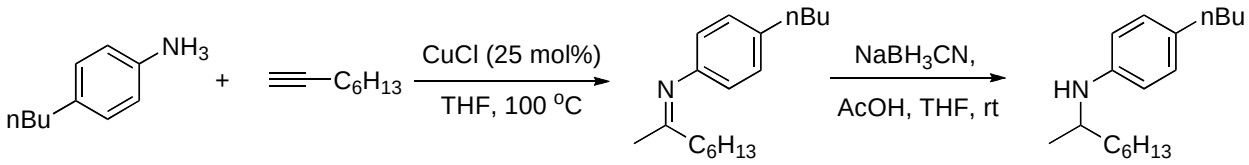


8.9 mg

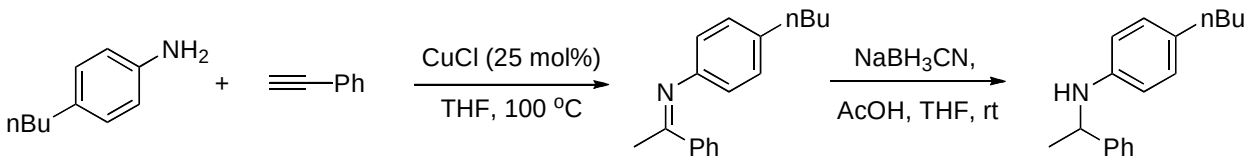
The same set of reactions with the same catalyst loading, temperature and time was then performed with all binary and ternary combinations of the four substrates in the two second generation groups that led to product. The results are shown in the following table.

Reaction #	Reactant	Product Detected by GC-MS?
1	1,2	No
2	1,3	No
3	1,4	No
4	2,3	No
5	2,4	No
6	3,4	Yes
7	1,2,3	No
8	1,2,4	No
9	1,3,4	Yes
10	2,3,4	Yes

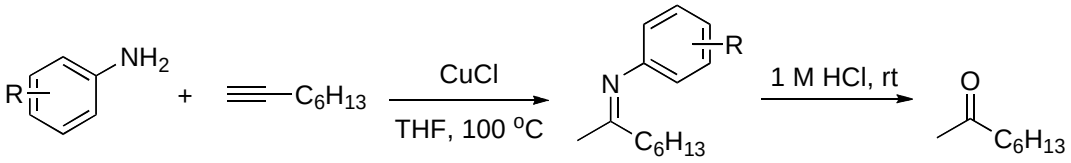
From these results, it was determined that the product was formed from Reactant 3 (diphenylacetylene), and Reactant 4 (4-*tert*-butylphenylboronic acid). An independent reaction with phenylboronic acid and diphenylacetylene catalyzed by 20% $Ni(cod)_2$ and 40% PPh_3 in THF formed triphenylethylene in 78% yield, as determined by GC and GC-MS, confirming the assignment of reactants leading to the product.



One-pot alkyne hydroamination and reduction with 4-*n*-Bu-aniline and 1-octyne. Inside a glove box, CuCl (24.9 mg, 0.250 mmol, 0.250 equiv), 4-nBu-aniline (224 mg, 1.50 mmol, 1.50 equiv), 1-octyne (110 mg, 1.00 mmol, 1.00 equiv), and dry THF (2 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 16 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC-MS. After full conversion of the alkyne was observed, $NaBH_3CN$ (189 mg, 3.00 mmol, 3.00 equiv) and 2 mL THF were added to the reaction mixture. The reaction mixture was cooled to 0 °C with an ice bath. AcOH (0.6 mL, 10 mmol, 10 equiv) was added dropwise to the reaction mixture. The ice bath was removed, and the reaction was allowed to warm gradually to room temperature. GC-MS analysis after 4 h indicated full conversion to the secondary amine. The reaction mixture was neutralized with aq. Na_2CO_3, extracted with EtOAc, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0-15% EtOAc in hexanes) to give the secondary amine product (177 mg, 68%). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.07 (d, J = 8.3, 2H), 6.61 (d, J = 8.4, 2H), 3.51 (dd, J = 6.1, 12.3, 1H), 3.27 (s, 1H), 2.60 (m, 2H), 1.65 (m, 4H), 1.45 (m, 11H), 1.25 (d, J = 6.3, 4H), 1.01 (dt, J = 7.2, 14.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.94, 131.48, 129.38, 113.45, 49.03, 37.62, 34.99, 34.31, 32.14, 29.68, 26.45, 22.92, 22.64, 21.14, 14.36, 14.27.



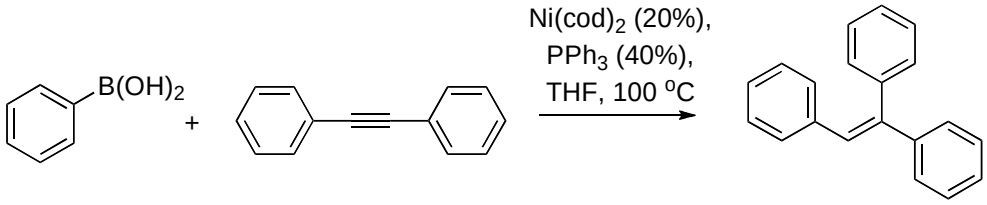
One-pot alkyne hydroamination and reduction with 4-*n*-Bu-aniline and phenylacetylene. Inside a glove box, CuCl (24.9 mg, 0.250 mmol, 0.250 equiv), 4-nBu-aniline (224 mg, 1.50 mmol, 1.50 equiv), phenylacetylene (102 mg, 1.00 mmol, 1.00 equiv), and dry THF (2 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 16 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC-MS. After full conversion of the alkyne was observed, $NaBH_3CN$ (189 mg, 3.00 mmol, 3.00 equiv) and 2 mL THF were added to the reaction mixture. The reaction mixture was cooled to 0 °C with an ice bath. AcOH (0.6 mL, 10 mmol, 10 equiv) was added dropwise to the reaction mixture. The ice bath was removed, and the reaction was allowed to warm gradually to room temperature. GC-MS analysis after 4 h indicated full conversion to the secondary amine. The reaction mixture was neutralized with aq. Na_2CO_3, extracted with EtOAc, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0-15% EtOAc in hexanes) to give the secondary amine product (138 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.1, 2H), 7.40 (t, J = 7.6, 2H), 7.31 (t, J = 7.3, 1H), 7.00 (d, J = 8.4, 2H), 6.54 (d, J = 8.4, 2H), 4.54 (q, J = 6.7, 1H), 3.99 (s, 1H), 2.55 (m, 2H), 1.60 (m, 6H), 1.41 (dq, J = 7.4, 14.8, 2H), 0.99 (t, J = 7.3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.82, 145.55, 131.92, 129.28, 128.92, 127.14, 126.18, 113.59, 54.03, 35.02, 34.30, 25.43, 22.68, 14.34.



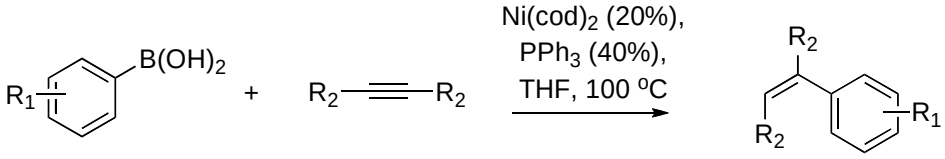
General procedure for copper-catalyzed alkyne hydroamination. Inside a glove box, CuCl (12.4 mg, 0.125 mmol, 0.250 equiv), an aromatic amine (0.75 mmol, 1.5 equiv), 1-octyne (56 mg, 0.50 mmol, 1.0 equiv), trimethoxybenzene, and dry THF (1 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 16-18 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC-MS. When full conversion of the alkyne was observed, 0.25 mL of 1 M HCl in H_2O was added to the reaction mixture and the mixture was stirred at room temperature for 4 h. After 4 h, the reaction mixture was analyzed by GC, and the yield of 2-octanone was determined by comparison to trimethoxybenzene, the internal standard, correcting for the response factor of the ketone to the standard.

Masses of aromatic amines and yields for copper-catalyzed alkyne hydroamination and hydrolysis.

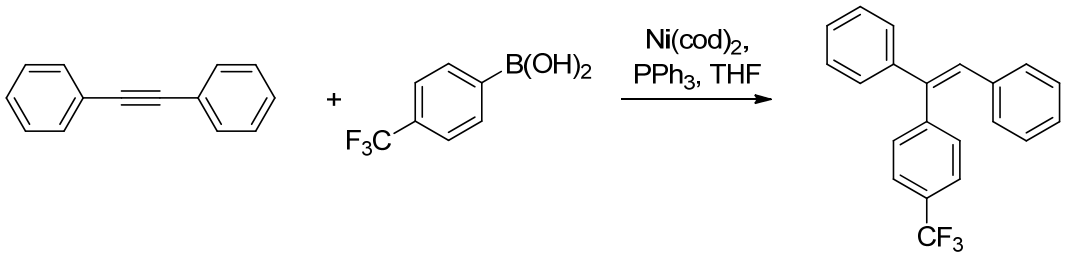
Aromatic Amine	Mass of Aromatic Amine (mg)	GC Yield of Ketone after Hydrolysis
4-nBu	112	77%
4-OH	82	80%
4-CN	89	51%
4-CO_2Me	114	68%
3-Br	129	84%
4-acetyl	102	60%
2,6-di-isopropyl	133	70%



Nickel-catalyzed hydroarylation of diphenylacetylene with phenylboronic acid. Inside a glove box, $Ni(cod)_2$ (5.5 mg, 0.020 mmol, 0.20 equiv), PPh_3 (10.5 mg, 0.040 mmol, 0.40 equiv), diphenylacetylene (17.8 mg, 0.100 mmol, 1.00 equiv), phenylboronic acid (36.6 mg, 0.300 mmol, 3.00 equiv) and THF (0.4 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 18 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC. The yield of triphenylethylene was determined by comparison to 1,3,5-trimethoxybenzene, the internal standard.

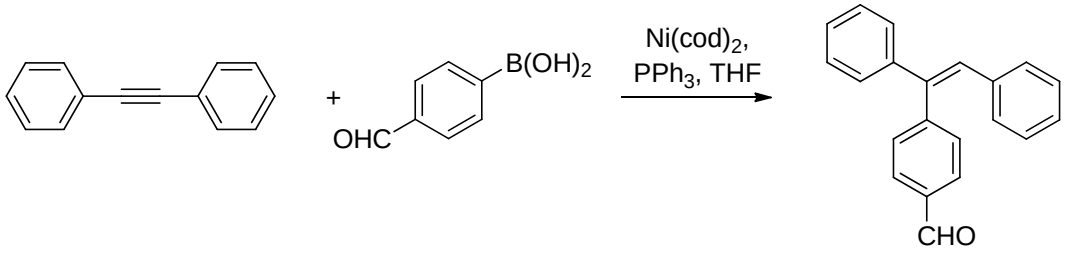


General Procedure for nickel-catalyzed hydroarylation of alkynes with aryl or heteroaryl boronic acids. Inside a glove box, $Ni(cod)_2$ (16.5 mg, 0.06 mmol, 0.2 equiv), PPh_3 (31.5 mg, 0.12 mmol, 0.4 equiv), alkyne (0.300 mmol, 1.00 equiv), arylboronic acid or heteroarylboronic acid (0.900 mmol, 3.00 equiv) and THF (1.2 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 18 h. After heating, the reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was then purified by column chromatography to give the product. The isomeric ratio (*Z:E*) was determined by comparison of GC peak areas.

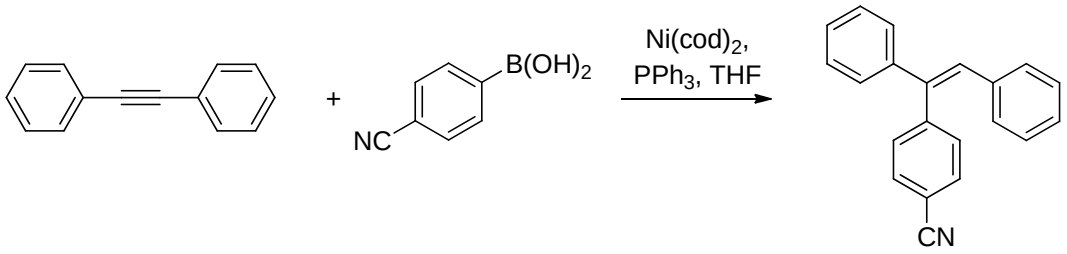


Nickel-catalyzed hydroarylation of diphenylacetylene with 4-(trifluoromethyl)-phenylboronic acid. Reaction performed according to the general procedure with 4-(trifluoromethyl)phenylboronic acid (171 mg) and diphenylacetylene (53.4 mg) to provide 88 mg of the product (91%) as a colorless oil. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 8.3:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3, 2H), 7.35 (m, 7H), 7.20 (m, 4H), 7.06 (m, 2H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 144.54, 142.94, 141.49, 137.07, 131.17, 130.49, 129.79, 129.64, 129.12, 128.94, 128.65, 128.43, 128.12, 127.89, 127.43, 126.77, 125.82, 125.79.

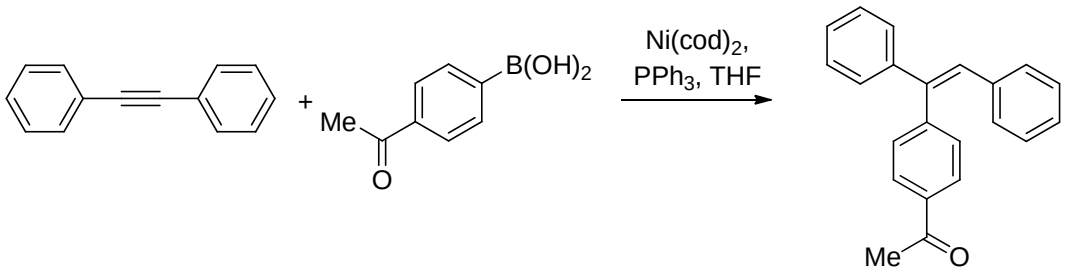


Nickel-catalyzed hydroarylation of diphenylacetylene with 4-formylphenylboronic acid. The reaction was performed according to the general procedure with 4-formylphenylboronic acid (135 mg) and diphenylacetylene (53.4 mg) to provide the 65 mg of the product (76%) as a colorless oil. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 11.8:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.85 (d, J = 8.1, 2H), 7.40 (d, J = 8.0, 2H), 7.31 (dt, J = 14.0, 22.6, 4H), 7.16 (dd, J = 5.9, 10.4, 4H), 7.04 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.22, 147.50, 142.81, 141.69, 136.98, 135.58, 131.54, 130.51, 130.26, 129.84, 129.80, 129.17, 128.66, 128.41, 128.15, 127.91, 127.49.

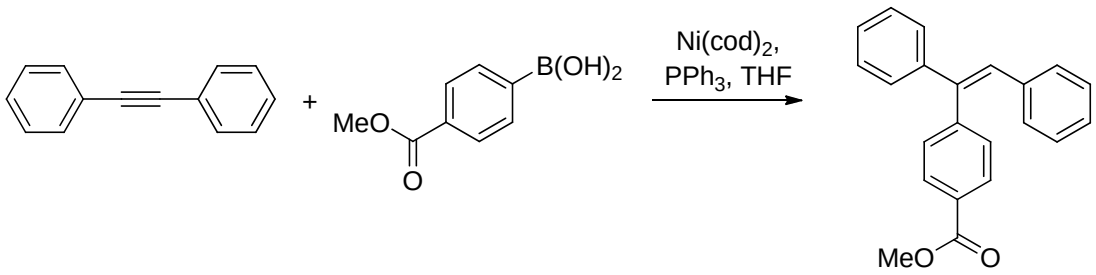


Nickel-catalyzed hydroarylation of diphenylacetylene with 4-cyanophenylboronic acid. The reaction was performed according to the general procedure with 4-cyanophenylboronic acid (135 mg) and diphenylacetylene (53.4 mg) to provide 52 mg of the product (62%) as a yellow solid. Column chromatography was performed with 10:90 ethyl acetate:hexanes. *Z:E* = >20:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.34

(m, 4H), 7.27 (m, 2H), 7.18 (dt, J = 3.1, 6.2, 4H), 7.04 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.83, 142.51, 141.16, 136.75, 132.61, 131.66, 130.16, 129.76, 128.72, 128.49, 128.28, 127.90, 127.63, 119.12, 111.40.

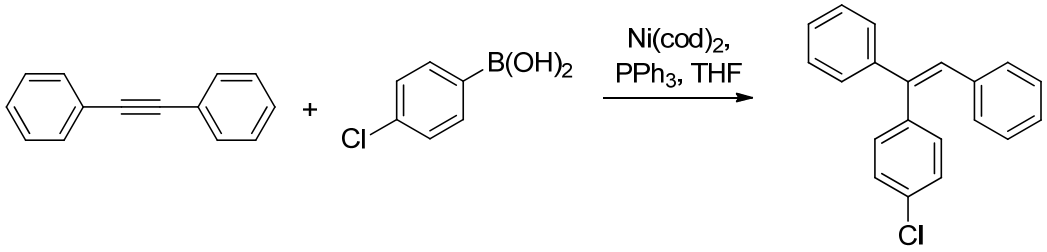


Nickel-catalyzed hydroarylation of diphenylacetylene with 4-acetylphenylboronic acid. The reaction was performed according to the general procedure with 4-acetylphenylboronic acid (148 mg) and diphenylacetylene (53.4 mg) to provide 65 mg of the product (73%) as a white solid. Column chromatography was performed with 10:90 ethyl acetate:hexanes. *Z:E* = 3.6:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2, 2H), 7.32 (m, 6H), 7.16 (dd, J = 5.0, 9.5, 2H), 7.05 (m, 5H), 2.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.08, 145.97, 142.97, 141.86, 137.09, 136.27, 131.04, 129.78, 129.51, 128.90, 128.59, 128.37, 128.05, 127.87, 127.36, 26.79.

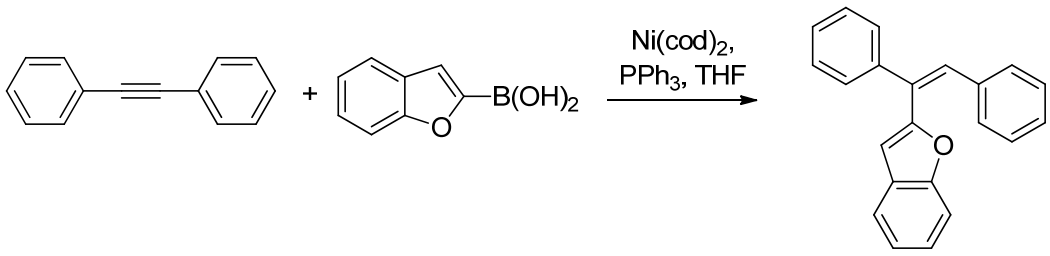


Nickel-catalyzed hydroarylation of diphenylacetylene with 4-methoxycarbonyl-phenylboronic acid. The reaction was performed according to the general procedure with 4-methoxycarbonylphenylboronic acid (162 mg) and diphenylacetylene (53.4 mg) to provide 85 mg of the product (90%) as a white solid. Column chromatography was

performed with 10:90 ethyl acetate:hexanes. *Z:E* = 3.2:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 3H), 7.37 (m, 6H), 7.19 (m, 3H), 7.06 (m, 3H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.31, 145.79, 142.99, 137.11, 133.17, 132.10, 130.86, 130.16, 129.94, 129.08, 128.59, 128.04, 127.87, 127.35, 115.49, 52.39.

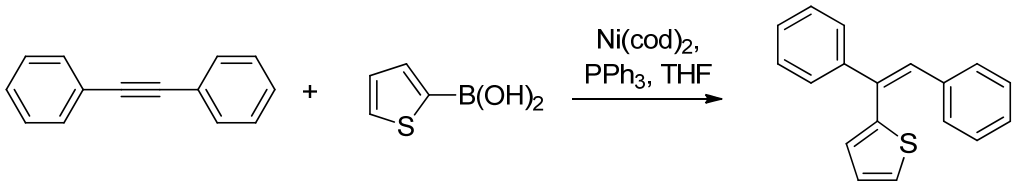


Nickel-catalyzed hydroarylation of diphenylacetylene with 4-chlorophenylboronic acid. The reaction was performed according to the general procedure with 4-chlorophenylboronic acid (141 mg) and diphenylacetylene (53.4 mg) to provide 72 mg of the product (83%) as a white solid. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 11.3:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.32 (m, 5H), 7.16 (m, 5H), 7.04 (m, 3H), 6.98 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.29, 141.59, 139.04, 137.27, 132.21, 129.75, 129.12, 128.99, 128.54, 128.35, 127.96, 127.87, 127.22, 126.75.

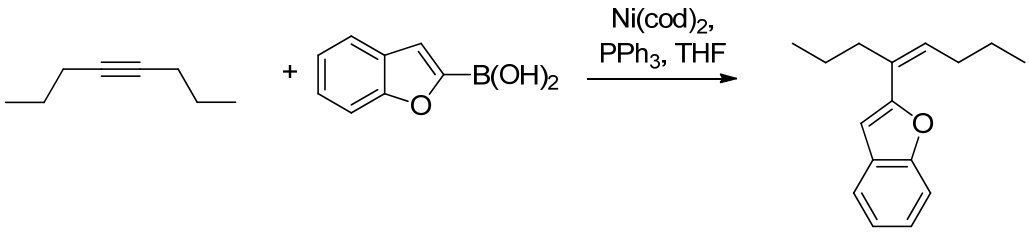


Nickel-catalyzed hydroarylation of diphenylacetylene with benzofuran-2-boronic acid. The reaction was performed according to the general procedure with benzofuran-2-boronic acid (146 mg) and diphenylacetylene (53.4 mg) to provide 84 mg of the product (95%) as a white solid. Column chromatography was performed with 5:95 ethyl

acetate:hexanes. *Z:E* = >20:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 9.0, 17.1, 2H), 7.48 (m, 3H), 7.42 (m, 2H), 7.33 (m, 2H), 7.29 (m, 2H), 7.22 (t, J = 7.4, 1H), 7.18 (m, 2H), 7.09 (dd, J = 6.7, 12.0, 1H), 6.27 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.18, 155.27, 137.76, 136.48, 132.75, 131.76, 130.26, 129.99, 129.22, 128.35, 128.32, 127.58, 127.56, 124.96, 123.10, 121.17, 111.19, 106.41.

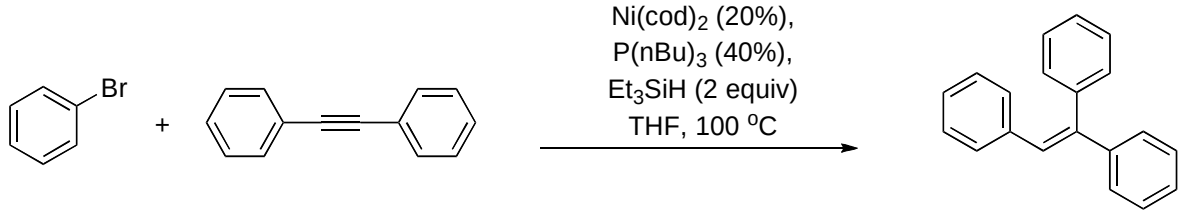


Nickel-catalyzed hydroarylation of diphenylacetylene with thiophene-2-boronic acid. The reaction was performed according to the general procedure with thiophene-2-boronic acid (116 mg) and diphenylacetylene (53.4 mg) to provide 70 mg of the product (89%) as a colorless oil. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 2.9:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.47 (m, 1H), 7.44 (m, 2H), 7.37 (m, 2H), 7.26 (m, 2H), 7.16 (m, 3H), 7.03 (dd, J = 2.2, 5.7, 1H), 6.99 (dd, J = 3.7, 5.0, 1H), 6.95 (dd, J = 0.8, 3.4, 1H), 6.79 (d, J = 3.5, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.22, 139.72, 136.91, 130.73, 129.72, 129.08, 128.49, 128.28, 128.12, 127.75, 127.11, 126.63, 126.38, 125.01.

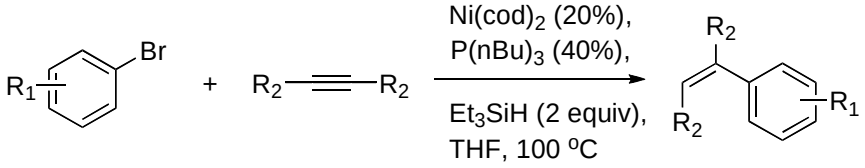


Nickel-catalyzed hydroarylation of 3-hexyne with benzofuran-2-boronic acid. The reaction was performed according to the general procedure with benzofuran-2-boronic acid (146 mg) and 3-hexyne (24.7 mg) to provide 33 mg of the product (55%) as a

colorless oil. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 3.7:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6, 1H), 7.45 (d, J = 8.1, 1H), 7.22 (m, 2H), 6.59 (s, 1H), 5.66 (t, J = 7.1, 1H), 2.49 (dd, J = 7.6, 15.2, 2H), 2.31 (m, 2H), 1.15 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.66, 154.77, 133.52, 130.89, 129.58, 124.02, 122.74, 120.72, 110.94, 101.07, 21.50, 21.47, 14.52, 14.47.

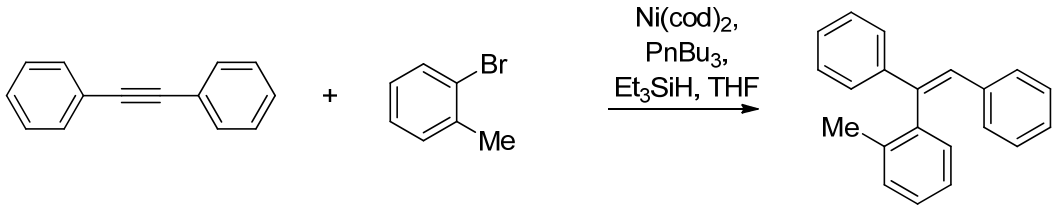


Nickel-catalyzed hydroarylation of diphenylacetylene with bromobenzene. Inside a glove box, $Ni(cod)_2$ (5.5 mg, 0.020 mmol, 0.20 equiv), $P(nBu)_3$ (8.1 mg, 0.040 mmol, 0.40 equiv), diphenylacetylene (35.6 mg, 0.200 mmol, 2.00 equiv), bromobenzene (15.7 mg, 0.100 mmol, 1.00 equiv), triethylsilane (24 mg, 0.20 mmol, 2.0 equiv) and THF (0.2 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 18 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC. The yield of triphenylethylene was determined by comparison to 1,3,5-trimethoxybenzene, the internal standard.

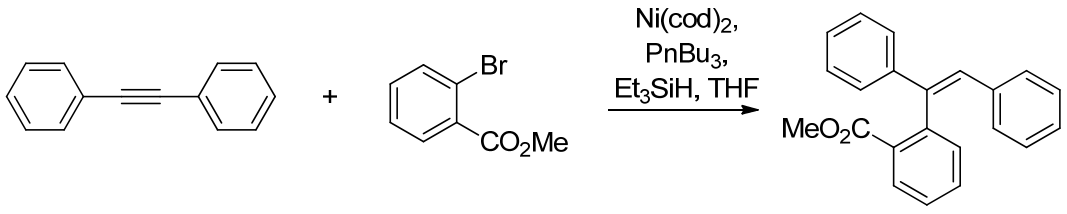


General procedure for nickel-catalyzed hydroarylation of diphenylacetylene with aryl or heteroaryl bromides. Inside a glove box, $Ni(cod)_2$ (16.5 mg, 0.06 mmol, 0.2 equiv), $P(nBu)_3$ (24.3 mg, 0.12 mmol, 0.4 equiv), diphenylacetylene (107 mg, 0.600

mmol, 2.00 equiv), arylbromide or heteroarylbromide (0.300 mmol, 3.00 equiv), triethylsilane (70 mg, 0.60 mmol, 2.0 equiv) and THF (0.6 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 100 °C for 18 h. After heating, the reaction mixture was cooled to room temperature, filtered through silica gel washing with EtOAc, and concentrated under vacuum. The reaction mixture was purified by column chromatography to give the product. The isomeric ratio (*Z:E*) was determined by comparison of GC peak areas.

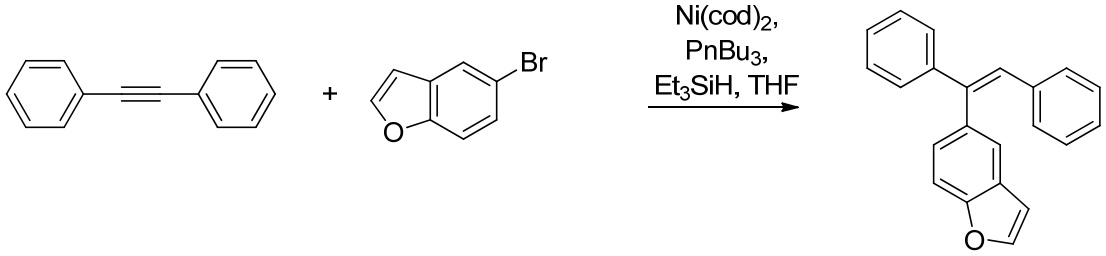


Nickel-catalyzed hydroarylation of diphenylacetylene with 2-bromotoluene. Reaction performed according to the general procedure with 2-bromotoluene (51.3 mg) to provide 44 mg of the product (54%) as a yellow oil. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 17.5:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.33 (m, 2H), 7.29 (m, 2H), 7.24 (m, 2H), 7.15 (m, 2H), 7.11 (s, 1H), 6.99 (dd, J = 1.6, 7.8, 2H), 2.08 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.56, 141.62, 139.90, 137.57, 136.87, 130.78, 130.43, 129.27, 128.94, 128.48, 128.35, 127.93, 127.63, 127.15, 126.84, 126.63, 19.92.

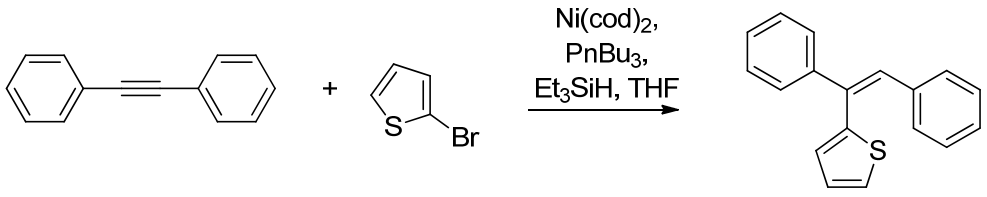


Nickel-catalyzed hydroarylation of diphenylacetylene with methyl 2-bromobenzoate. Reaction performed according to the general procedure with methyl 2-bromobenzoate

(64.5 mg) to provide 50 mg of the product (53%) as a yellow oil. Column chromatography was performed with 10:90 ethyl acetate:hexanes. *Z:E* = 4.2:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6, 1H), 7.65 (m, 1H), 7.44 (m, 3H), 7.25 (m, 5H), 7.12 (m, 3H), 6.98 (m, 2H), 3.58 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.70, 143.07, 142.61, 141.62, 137.51, 132.54, 132.48, 131.03, 130.22, 129.59, 128.43, 128.24, 127.88, 127.83, 127.57, 127.04, 126.96, 52.08.

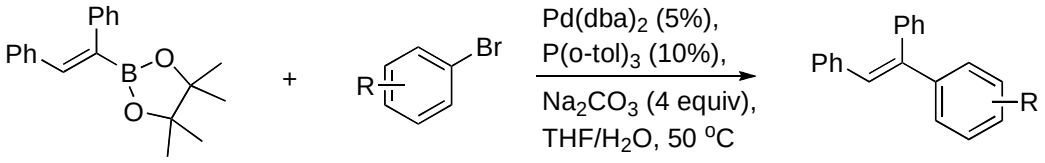


Nickel-catalyzed hydroarylation of diphenylacetylene with 5-bromobenzofuran. Reaction performed according to the general procedure with 5-bromobenzofuran (59.1 mg) to provide 61 mg of the product (69%) as a colorless oil. Column chromatography was performed with 10:90 ethyl acetate:hexanes. *Z:E* = 1.1:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.65 (m, 1H), 7.56 (d, J = 1.6, 1H), 7.49 (m, 2H), 7.36 (m, 5H), 7.28 (m, 3H), 7.08 (m, 2H), 7.04 (s, 1H), 6.74 (d, J = 8.0, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.87, 145.74, 143.13, 141.08, 137.82, 135.25, 130.72, 129.75, 128.88, 128.24, 127.94, 127.19, 126.85, 124.67, 123.24, 120.75, 111.89, 107.06.

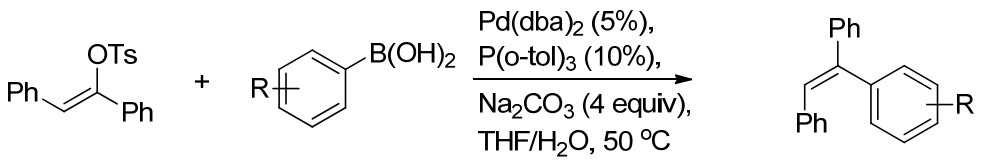


Nickel-catalyzed hydroarylation of diphenylacetylene with 2-bromothiophene. Reaction performed according to the general procedure with 2-bromothiophene (49.0 mg)

to provide 30 mg of the product (38%) as a colorless oil. Column chromatography was performed with 5:95 ethyl acetate:hexanes. *Z:E* = 5.4:1. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.55 (d, J = 7.3, 1H), 7.41 (m, 3H), 7.31 (m, 3H), 7.22 (m, 2H), 7.12 (m, 2H), 6.98 (m, 2H), 6.75 (d, J = 3.6, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.18, 139.67, 137.56, 136.86, 136.50, 130.14, 129.67, 129.03, 128.93, 128.23, 127.86, 126.75, 126.58, 124.96.



Determination of olefin stereochemistry. Inside a glove box, $Pd(dba)_2$ (1.4 mg, 0.0025 mmol, 0.050 equiv), P(*o*-tol)$_3$ (1.5 mg, 0.0050 mmol, 0.050 equiv), cis-stilbeneboronic acid pinacol ester (15.3 mg, 0.0500 mmol, 1.00 equiv), aryl bromide (11.3 mg, 0.0500 mmol, 1.00 equiv), sodium carbonate (22 mg, 0.20 mmol, 4.0 equiv), THF (0.2 mL) and degassed H_2O (0.04 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 50 °C for 18 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC-MS. The GC-MS retention times of the product from this Suzuki-Miyaura coupling reaction, which is the *E* alkene product, and the products from the alkyne hydroarylation were then compared. The GC-MS retention time of the triarylalkene product observed from this Suzuki-Miyaura coupling matched the minor product of the alkyne hydroarylation reactions. Therefore, the minor product of the hydroarylation was assigned as the *E* alkene product.



Inside a glove box, $Pd(dba)_2$ (1.4 mg, 0.0025 mmol, 0.050 equiv), P(*o*-tol)$_3$ (1.5 mg, 0.0050 mmol, 0.050 equiv), *Z*-1,2-diphenylethenyl tosylate (17.5 mg, 0.0500 mmol, 1.00 equiv), aryl boronic acid (0.0750 mmol, 1.50 equiv), sodium carbonate (22 mg, 0.20 mmol, 4.0 equiv), THF (0.2 mL) and degassed H_2O (0.04 mL) were added to a dry vial containing a magnetic stir bar. The vial was sealed, removed from the glove box, and heated at 50 °C for 18 h. After heating, the reaction mixture was cooled to room temperature and analyzed by GC-MS. The GC-MS retention times of the product from this Suzuki-Miyaura coupling reaction, which is the *Z* alkene product, and the products from the alkyne hydroarylation were then compared. The GC-MS retention time of the triarylalkene product observed from this Suzuki-Miyaura coupling matched the major product of the alkyne hydroarylation reactions. Therefore, the major product of the hydroarylation was assigned as the *Z* alkene product.

Picture 1 – Top View of Aluminum Well Plate with Glass Tubes used for Catalyst Screening

Picture 2 - Side View of Aluminum Well Plate with Glass Tubes used for Catalyst Screening

Picture 3 - Aluminum Well Plate used for Catalyst Screening with Top and Bottom Plates in place

6.6 References

(1) a) Eleuterio, H. S. *J. Mol. Catal.* **1991**, *65*, 55; b) Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 943.

(2) a) Stambuli, J. P.; Hartwig, J. F. *Curr. Opin. Chem. Biol.* **2003**, *7*, 420; b) Wieland, J.; Breit, B. *Nat. Chem.* **2010**, *2*, 832; c) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043; d) Boussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M.; Lund, C.; Murphy, V.; Shoemaker, J. A. W.; Tracht, U.; Turner, H.; Zhang, J.; Uno, T.; Rosen, R. K.; Stevens, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 4306; e) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 1413; f) Kinoshita, H.; Ingham, O. J.; Ong, W. W.; Beeler, A. B.; Porco, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 6412; g) Kanan, M. W.; Rozenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545; h) Rozenman, M. M.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 14933; i) Markert, C.; Rösel, P.; Pfaltz, A. *J. Am. Chem. Soc.* **2008**, *130*, 3234; j) Müller, C. A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3363; k) Teichert, A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3360; l) Szewczyk, J. W.; Zuckerman, R. L.; Bergman, R. G.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 216; m) Chen, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 2832; n) Hinderling, C.; Chen, P. *Int. J. Mass Spectrom.* **2000**, *195-196*, 377; o) Geysen, H. M.; Wagner, C. D.; Bodnar, W. M.; Markworth, C. J.; Parke, G. J.; Schoenen, F. J.; Wagner, D. S.; Kinder, D. S. *Chem. Biol.* **1996**, *3*, 679.

(3) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.

(4) a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668; b) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704; c) Francis, M. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 937.

(5) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904.

(6) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.

(7) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766.

(8) a) Zhou, L.; Jiang, H.-f.; Li, C.-J. *Adv. Synth. Cat.* **2008**, *350*, 2226; b) Han, J.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2009**, *132*, 916; c) Mu□ller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(9) a) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem. Int. Ed.* **1999**, *38*, 3389; b) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *ChemSusChem* **2008**, *1*, 333.

(10) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

(11) Xu, X.; Chen, J.; Gao, W.; Wu, H.; Ding, J.; Su, W. *Tetrahedron* **2010**, *66*, 2433.

(12) Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2008**, *14*, 11296.

(13) a) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474; b) Negishi, E.-i.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3151.

(14) a) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2008**, *74*, 973; b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961; c) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073; d) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.

(15) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.

(16) Quinton, J.; Kolodych, S.; Chaumonet, M.; Bevilacqua, V.; Nevers, M.-C.; Volland, H.; Gabillet, S.; Thuéry, P.; Créminon, C.; Taran, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 6144.

(17) Bellomo, A.; Celebi-Olcum, N.; Bu, X.; Rivera, N.; Ruck, R. T.; Welch, C. J.; Houk, K. N.; Dreher, S. D. *Angew. Chem. In. Ed.* **2012**, Early View.